VITAMINS

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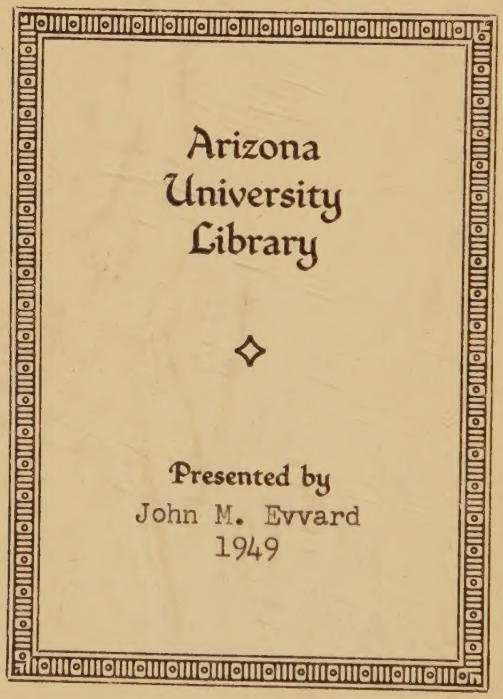

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VITAMINS

A CRITICAL SURVEY OF THE THEORY OF ACCESSORY FOOD FACTORS

BY

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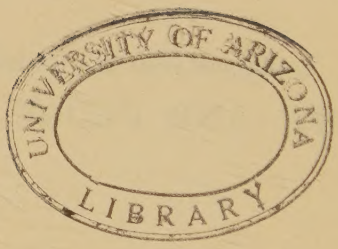

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TRANSLATORS' PREFACE

RAGNAR BERG's book marks the close of an epoch, the epoch during which the knowledge of vitamins was almost wholly confined to those who were engaged in the experimental study of the subject, and the epoch during which the data of the new science of nutrition were hidden away in the "transactions" of learned societies or scattered almost irrecoverably in the columns of polyglot periodicals. Berg has summarised all this matter within the compass of a single volume; has contributed new outlooks; and has provided a platform for the work of future investigators. Incidentally, he has written a book which, though adapted for specialist use, is anything but abstruse, and cannot fail to be of supreme interest to the general public—which is awakening to the importance of vitamins, and is in search of a guide through the dietetic labyrinth. There have been several attempts of late years to popularise the modern outlooks on dietetics. Notable among those in the English language are *Vitamins and the Choice of Food*, by Violet G. Plimmer and R. H. A. Plimmer (Longmans, London, 1922), and *Vitamines: essential food factors*, by Benjamin Harrow (second edition, Routledge, London, 1923). Either of these may usefully be read by the layman and the beginner as an introduction to the subject, but no serious student can afford to ignore Berg's masterly and comprehensive volume.

Our quotation of the respective titles of Harrow's and the Plimmers' books brings up the question of terminology. The word "vitamine" was introduced ten years ago by Casimir Funk (one of the pioneers in these investigations) to denote the antineuritic factor discovered and partially isolated by him. He chose the name in the belief that the substance belonged to the class of chemical compounds known

as "amines" or "amins." We follow good precedent in dropping the mute "e" from the word used as the title of Berg's book. But this does not solve the difficulty occasioned by the extension of the term vitamin to denote a whole class of substances most of which certainly contain no nitrogen—whether "Funk's vitamin" does so or not. That is why some authorities prefer to speak of these substances as "accessory food factors," and this name is used in the title of an excellent governmental publication (*Report on the Present State of Knowledge concerning Accessory Food Factors*, H.M. Stationery Office, 1921). But the proposed name is worse than cumbrous; it is vague; it might just as well describe the contents of an ordinary cruet-stand. The vitamins A, B, C, etc., are doubtless "accessory food factors"; but so are pepper, salt, and mustard; so is the "roughage" without which we should perish even though our food were to contain an abundance of proteins, fats, carbohydrates, and salts, together with an overplus of vitamins. Ragnar Berg therefore proposes to restrict the use of the word "vitamin" to Funk's vitamin (or vitamins), and to speak of the general class of substances to which the antineuritic principles, the antiscorbutic principles, the growth-factors, etc., respectively belong as the "complettins." Thus the general name for the *maladies de carence*, the deficiency diseases, is to be, not "avitaminosis," but "acomplettinosis." And our author is fairly successful in his attempt to be consistent in the use of his own terminology. But it will be noted that the title of his book is *Vitamins*, although the exhaustive chapter on "Beriberi and other forms of Polyneuritis," which is a detailed study of the nature and action of Funk's vitamin or vitamins, occupies only one fifth of the volume.

Here, in fact, as so often, usage rides rough-shod over attempts at linguistic purism. The picturesque word "vitamin," as a general term, has come to stay. The current employment of a word rather than its derivation, or its definition by a precisian, ultimately decides its meaning. The public imagination has been fired by the idea of these substances so recently discovered, so absolutely essential to *life*. In the first syllable of the word "vitamin" there is an appeal to a universal effect, to the instincts of

self-preservation and species-preservation. That is why both "accessory food factors" and "complettins" are likely to pass into oblivion; that is why even the inventor of the latter term finds it desirable to entitle his book *Vitamins!*

But the work covers a wider field than even this title might at first seem to suggest. The subject shades into others at the edges, and the action of the accessory food factors cannot be considered in isolation. This is where Berg's own important contributions to the new theory of dietetics have their place. For Ragnar Berg is no mere book-compiler; he is an original investigator, a biological chemist. As he good-humouredly remarks more than once, the dietetic experimentalists sometimes stray into error simply for lack of a competent chemist at their elbow. His own specialty has been "inorganic metabolism"; the bio-chemistry of inorganic acids, alkalies, and salts. Continually, in this book, he stresses the importance of an excess of bases (and suitable bases) in the diet, and shows how there has been increasing recognition of the extensive part played by acidosis as a contributory factor in the causation of many of the deficiency diseases. Agriculturists have long been familiar with the deleterious effects of "sourness" in soil. What we have to realise is that we can make the "soil" of our own tissues "sour" by such simple and everyday errors in diet as an immoderate consumption of table vinegar or of lemon juice, with consequent grave impairment of health. Acidosis, moreover, probably plays a part side by side with "acomplettinosis" or "avitaminosis" in reducing our power of resistance to various infective agents, and thus indirectly contributes to the onset of quite a number of diseases. Apart from the deliberate ingestion of acids, there is, as Berg repeatedly insists, another main cause of acidosis, and this is the faulty method of preparing food—especially vegetable food. Plant tissues contain a notable excess of bases. If we boil vegetables, and find no better use for the cooking water than to flush the drains with it, the natural alkalinity of the tissues of those who live largely on vegetables thus prepared will soon be lowered to the danger mark. In like manner, the boiling of milk reduces to a formidable degree the calcium content of that nutrient, and the calcium deficiency thereby determined

appears to be a contributory cause of rickets and other deficiency diseases.

Another point in which Berg is an innovator relates to the number of the vitamins or complettins. Hitherto most authorities have spoken of three only. Writing in 1922, Leonard Williams says (*Encyclopædia Britannica*, twelfth edition, vol. xxxii, p. 931): "There are probably a great many vitamins in natural foods—live or quick foods as they are called—but up to the time of writing three only have been isolated. These are: (1) the antiscorbutic factor; (2) the water-soluble B; (3) the fat-soluble A." Only three vitamins are considered by the Plimmers and by Harrow in the books already mentioned—although Harrow, in the appendix to his second edition (p. 245), does indeed refer to Casimir Funk's recent contention that "vitamin B is really a mixture of two vitamins, which he proposes to call vitamin B and vitamin D." Similarly McCarrison, one of the most noted investigators in this field, writes as follows in his *Studies in Deficiency Disease* (Henry Frowde and Hodder and Stoughton, London, 1921, pp. 244–245): "I have written of three vitamins, because three are known, not because it has been proved that there are only three. But whether there be only three or legion, they will be found to exist—and this is the important point—in the foods made in nature's laboratory, in quantities and combinations adequate for the due digestion and assimilation of the natural foodstuffs with which they are associated in nature. The subdivision of vitamins into many classes is not without the risks attendant on decentralisation. Vitamins, like other essential constituents of the food, are not to be regarded as independent of the assistance derivable from their associates in the maintenance of nutritional harmony. Each vitamin is but a member of a team, and the team itself but part of a co-ordinated whole."

Now Ragnar Berg is well aware of the importance of this conception of team work. (And, like McCarrison, he repeatedly stresses the perpetual interaction between the "team" of the vitamins and the "team" of the various endocrine glands in maintaining the balance of healthy nutrition.) But he thinks that the time is ripe for a somewhat more elaborate differentiation of the complettins. Provisionally, therefore,

he distinguishes five groups. The table showing our present knowledge of the complettin content of the various foodstuffs (pp. 328–331) is arranged in as many columns. The first of these deals with vitamins in the narrower sense of the term, and shows the richness of the different nutrients in Funk's vitamin (or vitamins, for Berg opines that they are multiple), which is the chief antineuritic principle of the food. Next—though not in the order named—come columns showing the quality of the foodstuffs as concerns their richness in the complettins which, pending their elusive isolation and a determination of their chemical composition, are known by letters of the alphabet: A, fat-soluble, often referred to as the antirachitic principle; B, water-soluble, whose predominant importance according to Berg is as growth-factor; C, water-soluble, the antiscorbutic principle; and D, water-soluble, differentiated by Berg both from B and from Funk's vitamin or vitamins, but like the latter functioning mainly as an antineuritic.

So much for the outlook upon the problem from the point of view of the *substances* known as vitamins, complettins, or accessory food factors. But Berg also considers the topic fully from the point of view of the deficiency *diseases*. First, of course, comes beriberi with the other forms of polyneuritis, for it was a study of these disorders which initiated the new science of dietetics. Arrest of growth demands a special chapter, and as an appendix to this comes a discussion which throws a little light on the nature of the still obscure tropical disorder known as psilosis or sprue. Scurvy, naturally, has a chapter to itself. Rickets and osteomalacia, xerophthalmia and keratomalacia, receive full consideration in the chapter on the fat-soluble complettin A. The penultimate chapter deals with various forms of oedema as deficiency diseases, and establishes the substantial identity of the "malnutritional oedema" of wartime experience with the "famine dropsy" of India, with "ship berberi," and with "prison dropsy." The concluding chapter is devoted to pellagra, and to the author's final summary of the whole position of the enquiry at the date of his writing. How recent this is may be deduced from the fact that his bibliography of more than 1,500 entries is carried well on into 1922, and that on pp. 326–327 he quotes

a passage from Sherman and Smith's book *The Vitamins*, published in New York only last year.

Apart from these " major " ailments which are classed in the nosology as definite " diseases," Berg's presentation of the evidence abundantly confirms the contention of those dieteticians who hold that an enormous amount of " minor " ill-health is due to what French writers have termed *carence fruste* or *hypocarence*. Many, perhaps most of us, suffer, not only in wartime, but under the comparatively favourable conditions of peace dieting, from what may be termed " larval deficiency diseases "—or from the effects of such diseases during our infancy and childhood, or from the effect of such diseases in our progenitors. On the paper cover of Otto Rühle's book *Das proletarische Kind* (The Proletarian Child, Langen, Munich, 1922) is a picture of two children who might be matched from any slum district of Europe or America. Both have the typical facies of acomplettinosis in childhood. The originals of these portraits would probably be found to present the stigmata of rickets ; but, short of actual rickets, *hypocarence* causes stunting of poorer urban children as compared with the children of the well-to-do. Yet even the latter are stunted, thanks to the futility of our " civilised " methods of preparing food. Take, for instance, Berg's statement on p. 189, based on the observations of Delf, Aron, Erich Müller, and others, that " in children . . . supposed to be thriving, to supplement the diet by fresh vegetables, extract of green vegetables, extract of carrots, or extract of bran, could always bring about a further increment of growth. These observations show how defective the nutrition of our children must be in contemporary life, even under what appear to be favourable conditions."

McCarrison, in especial, has emphasised the importance of this aspect of the new science of dietetics. He says we must always be on the look-out for avitaminosis, thanks to the pestilent way in which we habitually denature our food. " It seems to me that ' loss of appetite ' is one of the most fundamental signs of vitaminic deprivation. It is a protective sign : the first signal of impending disaster. It should at once excite suspicion as to the quality of the food in any patient who may exhibit it " (op. cit., p. 57).

The doctors of an earlier generation, who practised among those prone to overfeeding, used to say " we dig our graves with our teeth." But contemporary diet is just as likely to err by defect as by excess, and there is equally good reason to say that the foundations of premature death are laid in the flour-mill and in the kitchen, by the various processes with which profit-hunters and ignoramuses spoil our foods. " Fire is a good servant but a bad master," and man must learn to use fire less on his food and to use it more wisely, if he wishes to enjoy the best of health. Every intelligent reader will draw his own conclusions as to the practical application of the new knowledge to the regulation of his own diet. If a simple formula be requisite, it may be enough to quote McCarrison once again (p. 244) : " There are no more important ingredients of a properly constituted diet than raw fruit and vegetables, for they contain vitamins of every class, recognised and unrecognised." If a crucial example of the sort of thing to avoid be desired, take that cited by Berg (p. 268) from McClendon. The craving for fresh nutrients, says McClendon, undoubtedly has a survival value. " Among the American soldiers in the trenches, when their rations were restricted to chocolate, eggs, dried milk, and sugar, worked up into a sort of biscuit, he noted that this craving became overpowering within two or three days, and led them to refuse their rations." (Apparently the idea of the U.S. army authorities was that soldiers in the front trenches were like Robots. " You can feed them on pineapples, straw, whatever you like. It's all the same to them ! ")

Many of us go through life with no serious risk of rickets or osteomalacia ; we shall not get scurvy unless we visit the South Pole or the Klondike ; our chance of beriberi or malnutritional oedema is infinitesimal. But perhaps most of us suffer at one time or another from deficiency diseases ; perhaps all of us, under extant conditions, are affected during the years of growth by *tares* which are wrongly supposed to be *tares héréditaires*, or due to " weakness of constitution." Many of these troubles are, indeed, due to the follies of our parents or our parents' parents ; but they are by no means instances of " the inheritance of acquired characters," and yet quite as definitely as congenital syphilis they are cases

in which "the fathers have eaten sour grapes whereby the children's teeth have been set on edge." As a signal example, take that of the fowls which produced yolkless eggs after a "larval" deficiency in the diet had been operative for several generations (infra, p. 72). Perhaps one of the most significant passages in the work of which we now present the translation, is that on pp. 173–174 wherewith we may fitly conclude our preface: "The disastrous results of the present methods of child-feeding in our large towns should suffice to convince anyone that the period of observation [in experimental dietetics] should be much longer than is now customary. If we are to draw sound conclusions as to the value of any particular diet, it is not enough that we should be able to show that one individual apparently thrives on it. Osborne is right in maintaining that in many cases the effects of errors of nutrition do not become noticeable for three or four generations, and the assertion has been endorsed by numerous other investigators. *How many instances of so-called degeneration, of anatomical hindrances to childbirth, of incapacity for procreation, conception, lactation, etc., are referable to dietetic errors in earlier generations!*"

EDEN AND CEDAR PAUL.

July, 1923.

VITAMINS

CHAPTER ONE

INTRODUCTORY

From the days of Liebig down to the year 1910, only four classes of nutritive substances were recognised: proteins, fats, carbohydrates, and salts. It is true that Liebig already drew attention to the fact that development cannot run its normal course, either in plants, or in animals, should the supply even of one of the necessary constituents of a complete diet be inadequate. *The development of living beings is regulated by the supply of whichever element is least bountifully provided. In a word, this is the "law of the minimum."* So preponderant, however, is the importance of protein as the main factor in the building up of cell substance, that investigators speedily came to overlook all other matters, and to concentrate upon the supply of protein. Rubner, therefore, took a great step forward when he proved that it is not enough to furnish a sufficiency of protein, and that our aim must be to provide the body with the requisite modicum of energy. But here was a new fundamental principle to monopolise attention. As soon as a definite relationship between the nitrogenous and the non-nitrogenous nutritive elements had been experimentally established, the general belief prevailed that the edifice of the doctrine of nutrition had at least been finished in the rough. The various rooms of the structure might still require decoration, but no one anticipated any further extensive additions to the general body of knowledge.

In this reckoning, the fourth class of nutritive substances was, however, entirely overlooked. The inorganic constituents of the food, or, as they are usually named, the nutritive

salts, had been so much discredited by the unproved assumptions of unqualified curemongers and quacks and by the premature practical application of their ungrounded theories, that no one ventured to undertake serious research in this field. I myself, more than half a generation ago (instigated thereto by the pioneer work of my sometime chief, the revered Carl Röse), emphasised the importance of the inorganic constituents in nutrition. But whereas people were quite prepared to recognise that the law of the minimum was valid in the case of carbohydrates, and even in the case of fats, no less than in the case of proteins, there was little inclination to admit the practical working of the same law as far as the inorganic constituents of food were concerned. The amount of the total ash, the amount of sodium chloride, and subsequently too the amounts of calcium and of phosphates, were considered—these were the only inorganic constituents to which any attention was paid. It was at most conceded on the theoretical plane that the so-called ash contains a number of other substances which must be included among the genuine nutritive elements. The practical inference from this admission, that the law of the minimum must be valid in the case of every one of these additional substances, was sometimes disputed but more frequently ignored.

The most grievous defect of the old theory of nutrition was the way in which that theory overlooked the universal validity of the law of the minimum. Investigators ignored the extent to which every tissue builder is dependent upon all the others. They failed to realise that what is decisive for development is, not so much the absolute quantity of the various nutritive elements, as their relative proportions. They did not understand that the bodily need in respect of any one constituent of a diet can be determined only when we simultaneously take into account all the other factors of nutrition.

An additional defect, one to which I called attention fifteen years ago, was that in experiments concerning nutrition the duration of the experiment had invariably been far too short. My own experiments lasted at first for a week. Subsequently I extended them to a fortnight, and ultimately to several months. It thus became evident to me how intimate

is the connexion between the individual constituents of our diet. I learned that it is impossible to ascertain the body's need for any one substance, or to learn the way in which that substance acts upon the body, unless all the other constituents of the diet are being supplied in optimal quantities.

The third defect in the earlier study of nutrition was, finally, the primary assumption that the ordinary diet of civilised peoples contains all the necessary constituents in the necessary quantities. This assumption was supposed to be confirmed when in the course of a brief experiment no immediate or considerable loss of weight could be detected. It became the practice, therefore, to adopt as the basis of experiments upon the requisites for nutrition the very thing which had to be proved; the average supply of the various constituents of a customary diet was assumed to represent the bodily need for these constituents.*

The present work was begun in 1920, when we were entitled to celebrate the decennary of a new epoch in the doctrine of nutrition. In 1910 the liveliest antagonism would have been aroused by the assertion that our diet contained, in addition to the familiar four classes of food constituents, quite a number of other substances of a still unknown nature, substances absolutely essential to the welfare of the organism. When Schaumann here in Germany first began to speak of such essential accessory food factors, I was for a long time adverse to the assumption, and I attempted to explain the phenomena attributed to the alleged accessory food factors as the effects of the inorganic constituents of our diet, these being my own particular hobby. It seemed incredible that accessory food factors could have been overlooked for three quarters of a century. Beyond question we were only at the beginning of our knowledge of the effects of the inorganic constituents of food, and many surprises must still await us in this field

* This is the method which Rubner has employed quite recently when endeavouring to ascertain whether the wartime and post-war diets of Germany contained a sufficiency of calcium. He simply assumes that the pre-war diet both of Germany and of Japan was adequate in this respect, and thus his comparisons enable him to draw the conclusion that our present diet contains enough calcium. Unfortunately, not only does he use for his calculations estimates of calcium content which are sometimes erroneous and sometimes mere assumptions, but he likewise overlooks the fact that specialists have repeatedly proved that the pre-war diet was deficient in calcium!

of research. Even at that date, however, there were already numerous indications, merely awaiting confirmation, that the foregoing explanation was inadequate. First of all there was the evidence that the substances in question were present in almost infinitesimal quantities, like those of a homeopathic medicine; secondly there was the fact that these substances were thermolabile, were easily destroyed by heat. We knew, indeed, that the application of moderate heat to foodstuffs could exercise an influence upon the inorganic constituents of a diet. For instance, we knew that when milk is heated for too long a time the complex carbophosphates of calcium and magnesium undergo decomposition, and that a precipitate of insoluble carbonates and phosphates is deposited upon the wall of the containing vessel. These thermolabile salts are essential to the body of the new-born infant; their withdrawal from the milk leads to a deficiency of lime in the food, and this may endanger the life of the nursling. But if such withdrawals of inorganic substances from the food are to have a decisive influence upon nutrition, the quantities must be measurable in centigrammes or even in decigrammes, whereas the antineuritic constituents of the food produce notable effects in quantities of milligrammes or fractions of a milligramme.

When yet other classes of food-constituents had been discovered, having an analogous but nevertheless specifically different influence upon nutrition, my hypothesis became untenable. I was forced to admit that our diet must contain small but very important quantities of many hitherto unknown kinds of substance. The chief reason why they were not discovered sooner is one that has been already indicated—the unduly brief duration of experiments upon nutrition.

During the last few years, the literature embodying the results of these researches has attained considerable proportions. The world war, and the consequent severance of the nations, have however greatly hindered the growth of knowledge. It has been impossible for the individual investigator to keep himself adequately informed concerning researches similar to those upon which he himself was engaged. Especially in Germany have we suffered from this lack, and that is certainly one of the reasons why the Germans have been so

greatly outstripped in the field of study we are now considering —although Germany may be regarded as the scientific fatherland of vitamin research. Hence the German publications during the war had in most cases been long forestalled by the American, to say nothing of the fact that the writings of the German investigators lacked the fertilising influence resulting from the study of foreign models. Furthermore the literature of the subject is very widely dispersed, so that years of work are requisite to secure a competent knowledge of what has been achieved.

Since from the very outset I took a keen interest in these researches, I have been able to secure a fairly complete collection of the relevant literature. For this reason, at the close of the first decennium of the investigation, I feel entitled to attempt a comprehensive survey of all that has hitherto been learned concerning vitamins. It must be admitted that the task is almost beyond the powers of any one person, seeing that at least a cursory knowledge is essential in the most diverse fields of chemistry, physiology, internal medicine, pathology, and morbid anatomy. In view, further, of the confusion that prevails upon this subject, it should hardly be necessary for the author to plead for the reader's indulgence. Such a first attempt will hardly be free from a few mistakes.

The confusion to which I refer is extremely conspicuous in the matter of nomenclature. At the outset of these researches, when investigators were still almost exclusively concerned with beriberi and the kindred experimental polyneuritis, there was a certain justification for considering both the curative and the preventive effects of the newly discovered substances on parallel lines with the familiar medicaments. Consequently, each newly discovered substance (or rather, mixture of substances) received a special name. The first of such names was " X acid," used by Hulshoff-Pol in his papers of 1902 [38] and 1907 [68] for the antineuritic principle isolated from the bean katjang-idjo (Phaseolus radiatus). The earliest Japanese investigators who attempted to isolate the antineuritic substance likewise regarded it as an acid, and named it " aberi acid." [136] Funk, however, found that he was dealing with an organic base, and spoke of it as

" vitamin." As a matter of course, numerous attempts were promptly made to turn the new discoveries to practical account. A flood of antineuritic preparations invaded the market, and the tide is still rising. It was equally a matter of course that each of these preparations should receive its own patented designation. Thus we have: oryzanin [210]; torulin [220]; orypan [884]; antiberiberin [320]; oridin [1113]; sitacoid [714]; etc. Meanwhile, additional vitally essential nutritive elements were being brought to light, substances requisite to adequate nutrition. Röhmann [472, 522] therefore proposed to give them the comprehensive name of " accessory food factors " (Ergänzungskörper). The practical-minded Americans evaded the difficulties of nomenclature by refraining from the coinage of specific names; they were content to speak of " the fat-soluble factor A," of " water-soluble B," or " water-soluble C." Abderhalden [803, 1230] used the term " eutonin " to denote the antineuritic substances as a class, this implying the possession of a knowledge of their mode of action—a knowledge which is unfortunately still lacking. Equally unfortunate was this investigator's choice of the name " nutramin " for the water-soluble growth-complettin, seeing that this substance contains no nitrogen. Various other names have been suggested, with a varying measure of success. I may instance the ambitious " biophor " [1312] among the less successful efforts, inasmuch as every suitable constituent of our diet may be termed a " life-sustainer." Drummond,[1167] hoping to bring order out of chaos, has actually made confusion worse confounded by the proposal to use the oldest name " vitamin " for the accessory food factors as a class, to retain the term " vitamine " (this being the way in which the word has hitherto been spelt in England, although the Americans write " vitamin ") for Funk's antineuritic substance, and to drop the qualifying adjective " water-soluble " or " fat-soluble " in the case of the other substances.

There are several objections to this proposal. An objection to the use of vitamin as a collective name is that some of the substances under consideration contain no nitrogen, and therefore are certainly not amins. Further, it seems fairly certain that there is a second antineuritic substance, free from

nitrogen, and distinct from Funk's vitamin, though like that body it is readily soluble in water. But by the rules of priority the original name belongs to the substance which was given that name by its discoverer; and there can be no doubt that the use of the term vitamins, to denote a whole class of substances of this kind has, in actual practice, given rise to grave confusion. If, however, the antineuritic substances are to be known as vitamins, a still worse confusion will arise should the same term now be collectively applied to various other constituents of our diet. There is good ground for the contention that the misunderstandings still prevalent in the science of nutrition are mainly due to the improper use of the word vitamin. In physiological chemistry no less than in every other science it is essential that names should be perfectly free from ambiguity, that there should be no possible doubt as to their denotation. In view of these considerations, preference must be given to the collective name "accessory food factors," introduced by Röhmann, for this name implies no more than that the substances in question are essential complements of an adequate diet, that they are accessory to the four classes of foodstuffs with which we have long been familiar—proteins, fats, carbohydrates, and inorganic salts. But if this term is to secure acceptance in international science, it must be translated into the international language of science. In the present study, therefore, the author will use the designation "complettin." The term "vitamin" will thus be reserved (in conformity with Funk's original intention) for the nitrogen-containing antineuritic substances. Should any non-nitrogenous antineuritic substances be proved to exist, these must receive a distinct name. The water-soluble growth-promoting substance will be spoken of as "complettin B," bearing always in mind that it has very rarely been studied apart from the vitamins; the fat-soluble accessory food factor will be termed "complettin A"; and the antiscorbutic factor will be spoken of as "complettin C." This nomenclature will secure complete freedom from ambiguity.

The diseases that arise from a deficiency of the accessory food factors must be similarly dealt with in the matter of nomenclature. Funk [323] proposed to speak of these as "avitaminosis," but if the use of the name vitamin be

restricted to the nitrogen-containing antineuritic principle, it would be extremely misleading to speak of scurvy (scorbutus), pellagra, and similar disorders, as avitaminosis. For all these disorders due to a deficiency of one or more accessory food factors I shall, therefore, henceforward use the name "acomplettinoses"—the German vernacular equivalent being "Mangelkrankheiten," the French "maladies de carence," and the English "deficiency diseases." There is all the more reason for the use of such a collective designation, inasmuch as it is somewhat exceptional to find one of these morbid processes in a pure form. In most cases of deficiency disease there is more than one class of substances lacking, although the overwhelming lack of one or other of them gives the illness its specific stamp.

As already mentioned, the literature of the accessory food factors has now become so extensive that the individual investigator finds it barely possible to read without delay and to turn to practical account in his own work the publications that are poured forth almost daily from the press. Moreover, anyone who stands a little aside from the main current of research will often find it extremely difficult to decide to what extent an ostensibly new contribution really contains novel elements. In experiments concerning nutrition every detail is of importance. The most trifling change may revolutionise all the conditions of an experiment. In many instances authors fail to recognise, or do not recognise readily enough, the real source of the new or divergent results they report. This is only too natural. In earlier researches upon metabolism, students were content to consider the effects of proteins, fats, and carbohydrates; and when exceptionally scrupulous they would also take into account the result of a summary addition of salts. To-day we have further to make allowance for four or five accessory food factors; and in addition, in the modern and protracted experiments upon nutrition, we have to reckon with factors which in former days were completely ignored. The variety of protein employed, and its richness in tissue-building constituent, must be allowed for, although our knowledge of the composition of protein is still far from precise. There is not even one of the best-known proteins of which we can say that we

know all the factors requisite for its existence in perfection. Similarly as regards the fats, for we still do not know which of these substances are absolutely indispensable to the organism. Even more complicated is the problem of the inorganic constituents of nutrition, so manifold in their variety. From seven to ten metals at least and as many metalloids have to be taken into account. Each of these may exist in the animal body, either in ionisable (i.e. salt-like) forms, or else as a masked constituent of some extremely complex organic combination which is perhaps itself essential to life. For normal growth, for normal wellbeing, it is not enough to furnish by rule of thumb a diet containing certain quantities of all these substances. Liebig's law of the minimum applies to each individual substance, and in part to each type of substances. But the mutual relationships of the substances are so intricate that it seems almost hopeless to undertake researches concerning the individual minima.

The further back we go in the history of the accessory food factors, the simpler do we find the experiments to have been, but for the same reason the earlier technique was comparatively defective and the results were consequently more questionable. To-day such experiments, if they are to be rightly planned and if their results are to be correctly interpreted, demand the most careful and extensive preliminary consideration. Furthermore it is essential, in these protracted investigations, to make due allowance for what has been termed " the laboratory factor," whose importance has been quite recently recognised. We have to remember that the animals we are subjecting to experiment are living in confinement, and are therefore far more infirm and far more exposed to noxious influences than their congeners living in a state of nature. Especial consideration must be paid to the " cage-factor," to the physical conditions under which the animals are placed, not forgetting the circumstance that a monotonous and uniform diet is being enforced upon them. Purely psychical factors likewise affect the wellbeing of animals. For instance, in some animals, the mere taking out of the cage once or twice a week for weighing will make it impossible for them to thrive, even though their diet is all that can be desired.

If, therefore, we wish to appraise the upshot of individual experiments, we must bear in mind that the earlier investigations are often vitiated by errors which invalidate the entire result. It must also be remembered that not a few experimenters exhibit a certain mulishness, so that for one reason or another they will not modify a wonted method of conducting their researches, refusing to recognise or failing to understand the improvements made by a rival. To sum up, we rarely encounter perfectly unambiguous results. In many cases an acceptable result can only be secured after due allowance has been made for the defective conditions of the experiment, or after errors have been eliminated by comparison with the work of other investigators. In this task, the critic must not be frightened by any name, however illustrious. Why should he be frightened? The whole science is still in its initial stages, and only by making mistakes can we learn how to avoid them. Far be it from me to maintain that my own technique as critic is wholly free from objection, but only by strenuous though benevolent criticism can we hope to achieve something as near perfection as human beings can attain.

For several decades, Germany was the citadel of nutritive research. The most noted names in this domain, those of Liebig, Pettenkofer, Voit, and Rubner, are German. But precisely because their leadership had been so outstanding, the German science of nutrition became gradually enmeshed in rigid dogmas, which were ultimately regarded as indisputable. It has probably been for this reason that of late, in so brief a time, Germany has been hopelessly outstripped in the science of dietetics. The Germans are still dumbfounded at the revelation that there are nutritive substances that cannot be included in the familiar four classes, and that consequently all that has hitherto been learned concerning nutrition can have no more than conditional validity. We have in Germany so long been accustomed to regard protein as a uniform entity from the nutritive outlook, that we now find it extremely difficult to recognise in practice what has long been admitted as a matter of theory, namely that there are diverse sorts of protein and that their diversity of values must be recognised from the biological as well as from the chemical standpoint.

First of all, therefore, it will be necessary to study the latest views concerning the biological importance of the various proteins, that we may realise how fundamental this matter is in relation to the planning and the interpretation of experiments upon accessory food factors.

I have already emphasised my opinion that—owing to the fact that the importance of protein as a tissue builder, and the essential need for supplying energy for the maintenance of life, are so easily understood—there has been a widespread tendency to overlook and to ignore the importance of the inorganic salts, although this fourth great class of nutritive constituents has long been known to us. Let me insist once more that for these substances, too, the law of the minimum is fully valid. The results of earlier researches supply ample evidence of the physiological importance of the various inorganic ions. In the history of the evolution of our knowledge of accessory food factors, the value of the inorganic constituents of our diet repeatedly forces itself on the attention. We learn likewise that their interrelationships are vital to the effective influence, not only of the accessory food factors, but also of the three primary classes of organic nutritive constituents whose place in metabolism had been assumed to have been perfectly understood. These problems must also receive close attention, if we are to be enabled rightly to appraise individual experiments concerning accessory food factors.

What is true of philosophy and of history is equally true of the science of nutrition. The further we advance in our studies, the more vividly are we made aware of the way in which one happening is dependent on another. In the end we recognise as a fundamental principle that the significance of any occurrence can never be properly estimated in isolation. In such an estimate, all the cooperating factors must be taken into the reckoning before a final judgment is formed. In the science we are now studying, this principle applies to the problem of the bodily requirements of each individual nutritive constituent.

During the study of this book, the reader will perhaps find the innumerable references to authorities disturbing, and may be inclined to regard them as superfluous. Let him

remember that " the labourer is worthy of his hire," and that it would be unjust to mention some authors and leave others unnamed. Moreover, I have a personal reason for being precise in this matter of citation. When studying the processes of nutrition I have not infrequently been charged with ignorance of their medical and physiological aspects. Now that my ideas have been so widely and so thoroughly confirmed by modern dietetic researches, it is essential that I should specify which results are my own and which are those of other investigators. Failing this, the present work might simply be shelved as " the fantasies of a Berg or a Lahmann." My book would then fail to achieve its main purpose, which is to stimulate, the German study of the science of nutrition.*

* I must take this opportunity of explaining that the present directorate of Dr. Lahmann's sanatorium is nowise responsible for spiritual participation in my book. Far from it, for that directorate has repeatedly declared that Lahmann's teaching is now obsolete, and that enough work has been done as regards the inorganic nutritive constituents. I have therefore been dismissed, and my sometime laboratory has been given over to experiments more accordant with the spirit of the times—experiments à la Steinach. It follows that I am alone responsible for my ideas !

CHAPTER TWO

THE BIOLOGICAL VALUE OF THE VARIOUS PROTEINS

1. The biological Value of the Amino-acids

The reader must first be reminded that, according to the pioneer investigations of Emil Fischer and his pupils, the proteins are largely or mainly constituted out of ester-like amino-acids compounded to form polypeptids. It is remarkable to find how little variation there is in the composition of the most diverse sorts of protein. As yet only a small number of amino-acids have been isolated from the natural proteins. Here is the list of these, the conventional name being given in the left-hand column, and the structural name in the right-hand:

glycocoll	amino-acetic acid
alanin	α-amino-propionic acid
serin	β-oxy-α-amino-propionic acid
valin	dimethyl-α-amino-propionic acid
leucin	dimethyl-α-amino-butyric acid
isoleucin	methyl-ethyl-α-amino-propionic acid
asparaginic acid	α-amino-succinic acid
asparagin	the anhydride of the same
glutamic acid	α-amino-glutaric acid
glutamin	the anhydride of the same
arginin	δ-guanidin-α-amino-valerianic acid
ornithin	α, δ-diamino-valerianic acid
lysin	α, ϵ-diamino-capronic acid
cystin	α-amino-β-propionic acid disulphide
cystein	α-amino-β-propionic acid sulphhydrate
β-phenyl-alanin	β-phenyl-α-amino-propionic acid

tyrosin	oxy-phenyl-alanin
tryptophan	β-indol-α-amino-propionic acid
histidin	β-imid-azolyl-α-amino-propionic acid
prolin	α-pyrrolidin carbonate
oxy-prolin	oxy-α-pyrrolidin carbonate

Leaving out of consideration the anhydrides and cystein (which are in all likelihood no more than decomposition products formed in the course of the experiments), we are thus concerned with only eighteen amino-acids, out of which the innumerable proteins are constructed. Of course even this limited number of constituents gives ample scope for varieties in combination. Out of the eighteen amino-acids, no less than 6,708,373,705,728,000 proteins could theoretically be built up. Were we to take no more than ten of the amino-acids, with these we could form 595,071 varieties of protein. But the differences between the proteins do not depend solely upon differences in the arrangement of these particular constituents, for unquestionably most proteins likewise contain various quantities of other substances besides the amino-acids. Finally we have to reckon with structural differences, which must certainly arise during the formation of optically active amino-acids.

It has long been known that the digestion of proteins involves their decomposition, and that when the influence of trypsin is sufficiently effective this splitting-up may proceed as far as the formation of various amino-acids. Conversely, Abderhalden has been able to prove [452] that dogs can be quite as efficiently nourished upon completely disintegrated protein as upon protein in the natural state. It was, indeed, subsequently shown that during the process of normal digestion the disintegration of protein does not usually go so far as the formation of free amino-acids, being arrested in the polypeptid stage. Still, Abderhalden's experiments have demonstrated as a matter of principle that the animal organism is at any rate competent to build up its own specific proteins out of the requisite amino-acids. Quite a number of investigators had anticipated Abderhalden in this demonstration (though somewhat less drastically), inasmuch as in experiments upon animals they had shown that when a variety

of protein lacking in some constituent indispensable to normal growth is given as a food, this protein may be rendered biologically adequate by adding the desired constituent to the diet.

In the before-mentioned work, Abderhalden likewise proved that *certain tissue-building constituents of protein are absolutely indispensable to the body.* Above all, this is true of *l-tryptophan,* which cannot be substituted by any other products of protein disintegration. It is true also of *l-tyrosin,* which can be replaced by its antecedent l-phenyl-alanin, but not by any of the aliphatic amino-acids nor yet by the corresponding keto-acids. Thereby Abderhalden confirmed what Osborne, Mendel, and Ferry [225] had previously maintained, that *the animal organism is incompetent to effect "ring-closing" (cyclopoiesis).*

Glycocoll, which can easily be produced by the oxidation of alanin or even of serin, need not apparently be provided ready-made in the food. *Prolin,* again, which is readily producible in the body by the oxidation of histidin, need not be supplied if the last-named antecedent material be furnished in the diet in sufficient quantity. Finally, it was proved later that *l-cystin* is essential. But in my opinion it still remains to be ascertained whether this substance cannot be substituted by the corresponding sulphhydrate cystein, since the latter can unquestionably be oxidised to form cystin within the body.

Abderhalden was unable to show that *d-lysin, arginin, ornithin, l-histidin,* and *d-glutamic acid,* are indispensable.

In this chapter I have given the premier place to Abderhalden's researches because his name enjoys exceptional repute in Germany. But he was far from being the first to undertake experiments of the kind. In the United States, experiments in the artificial feeding of animals were long ago instituted. Osborne and Mendel, in particular, have made extraordinarily comprehensive and far-reaching researches in this field—researches which are directly related to Metschnikoff's views concerning "nutritive pills"; but the enquiry as to the validity of the theory was undertaken long before it had become widely known. Osborne and Mendel have been greatly interested in the question whether animals can

carry on their vital economy with the aid of comparatively simple means; whether, for instance, phosphorus in purely inorganic combination will suffice. In these experiments, as soon as their duration was extended over many days or several weeks, the varying biological importance of the different proteins began to become manifest. As early as 1912, Osborne and Mendel were able to prove that the diet must contain certain minimal quantities both of *tyrosin* and of *tryptophan*.[225]

In the work just mentioned, and again later,[349] these investigators showed also that *glycocoll* is not an essential factor in diet; Lewis,[653] and Lewis, Cox, and Simpson,[1183] came to the same conclusion. Contradictory, at first sight, is the statement of Nitzescu,[804] that the protein of maize is incompetent to promote proper growth, owing to its lack of tryptophan and its inadequate content of glycocoll and lysin; but the Rumanian forgot to make a control experiment, adding the aforesaid substances to the diet in order to ascertain if any or all of them were truly indispensable. I have already adduced theoretical grounds for the opinion that glycocoll is not essential, inasmuch as this substance has such a composition that it must be formed in the organism by simple oxidation out of all the other aliphatic *a*-amino-acids. Such, too, is the bearing of Ivar Bang's discovery,[508] that proteins poor in glycocoll, and perhaps also in alanin, have in the rabbit no effect upon the amino-acid content of the blood; these substances, when present in very small quantities, are promptly used for building up the protein of the animal body. When, on the other hand, foodstuffs rich in glycocoll were given, an increase in the amino-nitrogenous content of the blood ensued; obviously because, when the bodies rich in glycocoll or alanin were worked up within the animal organism, amino-nitrogenous substances were produced in excess of the needs of the tissues. It is well known that when an aliphatic carbon chain undergoes oxidation in the animal body, the oxygen seizes the terminal carbon atom—or, if this be already a carbonyl, the adjacent α-carbon atom. But an exception to the rule occurs when the α-carbon atom is linked to an amin group, as is the case in all the naturally extant aliphatic amino-acids. Then this atom is overpassed, the oxidation

affects the β-atom, and the chain is broken with the formation of $NH_2 . CH_2 . COOH$—glycocoll, to wit. There is, however, little likelihood that alanin can be formed in the body, seeing that in alanin the β-atom is not oxidised. Throughout the literature of the subject, in fact, we can find no indication that it is possible to dispense with alanin. Sure, indeed, tells us [1263] that the addition of alanin to a protein of very low nutritive value did not bring about any improvement. But in this experiment there were so many other unfavourable factors that the ineffectiveness of the addition of alanin does not justify any inference concerning the indispensability of that substance.

Just as, during the process of oxidation within the animal body, glycocoll must arise out of the aliphatic amino-acids, so, and for the same reason, must *prolin* arise out of histidin compounds as a terminal product of biological oxidation. In actual fact it appears that this amino-acid is not a vitally essential constituent of our diet,[1263] provided that a sufficiency of histidin be supplied.

Indispensable, on the other hand, are *valin*, *leucin*, and *isoleucin*. Leucin (amino-isocapronic acid) cannot be substituted by norleucin (normal amino-capronic acid).[1200]

As far as the so-called hexone bases are concerned, peculiar conditions appear to prevail, and the matter has not yet been cleared up. Numerous experiments seem to have shown beyond dispute that *lysin* is an essential dietetic factor, and that the animal organism must be supplied with considerable quantities of this substance. (Cf. 349, 432, 492, 550, 568, 598, 613, 634, 680, 804, 1095, 1200.)

It is different as regards *arginin* and *histidin*. When both these bases are lacking, normal development is impossible, and it is even impossible to maintain the body-weight. Nevertheless, although the two substances differ so greatly in composition (arginin has an open carbon chain, from which there is no prospect of passing to the heterocyclic histidin), Ackroyd and Hopkins [535] and Geiling [650] agree in reporting that adequate growth can be secured when either arginin or histidin is supplied in the absence of the other. The explanation perhaps is that the bodily requirements are very small in the case of both substances—for it is hardly

conceivable that either can be transformed into the other within the organism.

Cystin is of peculiar composition, and numerous observations have shown it to be indispensable to nutrition (see, however, the reservation made on p. 31). Even proteins rich in cystin, such as casein [653, 1183] and lactalbumin,[1264] acquire an enhanced nutritive value when small quantities of cystin are simultaneously administered.

Inasmuch as the animal organism seems to be incompetent to achieve cyclopoiesis, it is obvious that *phenyl-alanin* must be an indispensable factor of nutrition.[653] Mitchell records an observation to the opposite effect,[549] but in this experiment the administration of amino-acids alternated with periods of protein starvation during which amino-acids were of course being formed within the body. In hunger states these amino-acids are vigorously retained, and this may have falsified the results during the subsequent period when amino-acids were being supplied in the food.

It is equally obvious that *tyrosin* must be an essential dietetic factor; the requisite quantities of this substance are small,[653] but vitally important.[1264] Mitchell's observation to the contrary [549] is, as in the case of phenyl-alanin, explicable from the peculiar conditions of the experiment. As already said, the necessary amount is very small.[600] This is accounted for by Abderhalden's observation [452] that tyrosin (oxy-phenyl-alanin) is to some extent replaceable by its antecedent phenyl-alanin, which undergoes oxidation within the body. The oxidation of a benzol ring, so difficult to effect in the laboratory, is a familiar occurrence in the animal organism. I need only remind the reader of the transformation of benzol into phenol.

I have more than once insisted that *tryptophan* is an indispensable dietetic factor. On theoretical grounds it must be so, owing to the complicated composition of this substance, and owing to the incompetence of the human organism to synthetise carbon chains. The inference is confirmed by numerous observations. (Cf. 349, 535, 549, 561, 680, 804, 1095, 1263.) Thanks to the before-mentioned incapacity of the body, it is obvious that tryptophan cannot be replaced for dietetic purposes by its disintegration product cynuric acid.[531] Since the organism needs fairly large amounts of tryptophan, we

find that, when the proteins in the food contain only small quantities of that constituent, growth runs parallel, to a certain extent, with the tryptophan content.[492, 613] This partly explains the superiority of mother's milk to cow's milk for infant feeding, seeing that the lactalbumin of human milk is peculiarly rich in tryptophan. Although human milk contains a smaller percentage of protein than cow's milk, the absolute tryptophan content of the former is considerably larger.[1307] It is noteworthy that when there is a long-continued deficiency of tryptophan in the diet, the endocrine glands degenerate just as they do when there is a complettin deficiency. This will be further discussed in the sequel. Enough for the moment to point out the superlative importance, in experiments upon the effects of the complettins, of attending to the satisfactory composition of the dietetic proteins.[1055]

No investigations concerning *oxy-prolin* have come under my notice; but we can hardly be mistaken in assuming that, like tyrosin, it is replaceable by its unoxidised antecedent. In the case of oxy-prolin this antecedent is prolin, and perhaps also histidin. So complicated a substance, being heterocyclic, can hardly be replaced by any other food constituent than those just named.

Before closing this brief survey of the biological importance of the amino-acids, we must refer yet again to Mitchell's work,[549] which shows that during brief experiments even grave errors in diet can be compensated. Experimenting on white mice, Mitchell gave them a diet consisting of a mixture containing 34 % of starch, 28 % of protein-free milk (providing B, C, and inorganic salts), 10 % lard, 18 % butter (providing A), 6 to 7 % sugar, and 4 to 6 % of a mixture containing various amino-acids; this alternated with the same mixture except for the last-named ingredients, the amino-acids being replaced by a supplementary 10 % of sugar. He found that this alternation of a protein-free diet with one in which the protein content was manifestly inadequate gave better results than either the protein-free diet or the diet containing amino-acids given uninterruptedly. Obviously the defects in the composition of the amino-acid mixture (which when given unintermittently could not but lead to overfeeding with some of the amino-acids and to underfeeding with others) were miti-

gated in this way, that in the intervals when a nitrogen-free diet was given the body was forced to draw upon its own stores of material. We know that in such circumstances the most important constituents are vigorously retained by the body, and that on the other hand an intensive nitrogen hunger is induced. By these two factors, during the periods when the amino-acids were given to the white mice a better utilisation of the nitrogen was ensured than was possible in the instances in which the amino-acids were given unintermittently. Of course the organism's powers of self-help in this respect are strictly limited, and Mitchell could not keep any of the white mice alive for more than 98 days. We see, however, that in brief experiments the organism has numerous possibilities of self-help, numerous ways of compensating for defects in diet. Brief experiments, therefore, do not afford valid conclusions concerning the effects of an experimental diet. If gross fallacies are to be avoided, the experiments must be continued for so long a time that the sources of self-help in the organism run dry. Experiments upon the utilisation of proteins have commonly infringed this rule—especially when domestic animals have been the subjects of experiment. Thus only can we explain how, in Germany during the war, yeast (a substance of very low nutritive value as far as its protein is concerned) could be recommended as an adequate source of protein.

Inasmuch as the amino-acids can only be utilised by the organism in so far as the diet contains other constituents enabling these acids to be amplified into proteins proper to the animal under consideration, the supply (whether by mouth or hypodermically) of amino-acids that cannot be thus complemented is a useless burdening of the body. This is proved by the rise in the amino-acid content of the blood in such circumstances, and by the increased excretion of amino-acids in the urine.[508, 509]

In view of all these considerations, a discovery made by Abderhalden [452] is easy to understand : it is almost indifferent whether we give as food the protein specific to the animal concerned, or protein from some extraneous source ; on the other hand, the aggregate protein of an animal is greatly superior to the protein derived from any individual organ.

2. The Relationship of the proteid to the non-proteid nutritive Substances.

Of course in all such experiments the investigator must strictly observe the conditions that were found essential in the very earliest studies of protein metabolism. There must be an adequate supply of energy, measured with a liberal rather than with a sparing hand; and a suitable ratio must be preserved between the nitrogenous and the non-nitrogenous nutritive constituents. A vast amount of writing has been devoted to this ratio, and the most contradictory views have been put forward. Especially conflicting are opinions concerning the question whether nutrition can be adequately sustained by proteins and carbohydrates in default of fats, or by proteins and fats in default of carbohydrates. This problem is intimately connected with two others. First, can fats and carbohydrates be manufactured out of proteins? Secondly, are fats and carbohydrates really built up into the substance of the organism, or do they merely serve to supply it with energy?

The latter question is the more important of the two, for if fats and carbohydrates do not form essential constituents of the living tissues, their manufacture out of proteins is manifestly superfluous. Proteins unassisted could then provide for the requisite supply of energy. For a long time, physiologists were inclined to assume that fats and carbohydrates served merely as fuel or reserve. The German experience of war nutrition has, however, pointed towards the conclusion that fats have a certain value as tissue builders supplementary to their value as energy providers. It might be contended that the ailments attributable to a deficiency of fat in the diet were mainly due to a lack of fat-soluble A, and the inference might seem warrantable as far as the great majority of the population was concerned. But similar ailments occurred in vegetarians, despite their daily consumption of such foods as spinach and carrots, which contain large quantities of fat-soluble A. We are therefore led to infer that fats are indispensable as tissue builders.

The objector may still point out that symptoms of fat deficiency are not seen when there is a very liberal supply

of protein. But, on the one hand, almost all food rich in protein is also rich in fat (pulses, and even lean meat); and, on the other hand, it may now be regarded as proved that fat can be formed out of superfluous protein. The ill-effects of a fat-free diet can, therefore, only become apparent when the supply of protein is reduced to somewhere near the minimum. Unimpeachable experiments of such a character are not yet forthcoming.

However, the experience of various investigators accords with the data furnished by war dieting. Bierry [957] was led to the firm conviction that fats must actually serve as building materials in the animal organism, and that there must therefore be an essential minimum of fat in the food no less than an essential minimum of protein.[833, 973, 1106] A specialist in this field, Maignon, emphasises his view that the reason why it is so difficult to ascertain this minimum is that fats can be manufactured out of proteins within the animal organism.[744] On the other hand, the same investigator has found that a purely protein diet is directly toxic to the animal organism. The tonic influence is not solely explicable as the outcome of the effect of acids, for it cannot be prevented by the administration of alkalies; but it can be prevented by adding fat or carbohydrate to the diet.[778, 882, 883, 1081] Amar comes to the same conclusion.[779] Both Maignon and Amar opine that in these circumstances the fats have a protein-saving influence. Maignon [870, 903] attempts to explain this by suggesting that the missing amino-acids may by aminisation be formed out of the fatty acids. (An objection to this theory is, that the animal organism is incompetent to build up amino-acids out of fatty acids by aminisation.) There must, however, be contributory factors, for the toxic influence of the proteins exhibits marked periodicity; it is most apparent in spring and autumn, least apparent in winter and summer. Possibly the more vigorous growth that occurs during spring and autumn has a bearing upon this matter.[941, 1081, 1128] Carbohydrates, likewise, can counteract the toxic influence of proteins. Bierry, Maignon, and their pupils are all in agreement here.[778, 779, 833, 936, 957, 963, 973, 1039, 1106] The addition of lard to the extent of one-fifth of the weight of protein is already enough to improve the utilisation of the protein; but the best result,

namely nutrition with the lowest quantum of protein and of energy supplied, is secured when equal weights of protein and fat are given.[778, 883, 941, 1128] Furthermore, a similar improvement in the utilisation of proteins can be secured by supplementing them with carbohydrates; but in that case the supply of calories and the consumption of protein were higher with a diet containing equal weights of protein and starch than with one containing equal weights of protein and fat.[778, 941, 1128]

This view, that fats induce a better utilisation of proteins than carbohydrates do, is directly opposed to the opinions of Atwater, Mendel, and Levi; and it is contested by Terroine,[891] who, however, has no evidence to offer in rebuttal. Maignon,[870, 903] in order to explain this mode of action, assumes that there is increased formation of amino-acids out of both the glycerine and the fatty acids of the fats; the effect of carbohydrates is accounted for by their competence to supply the demand for energy.[936] Whereas it is difficult to believe that amino-acids can be newly formed out of either glycerine or fatty acids (see above), in my view the observed facts are readily explicable. We may suppose that, when fat is lacking, proteins must be used up for the formation of fat. Thereby, first of all, there ensues a greater consumption of protein; and, secondly, the consequent products of protein decomposition may very well account for the toxic phenomena that are witnessed in the bloodvessels and the kidneys, while simultaneously (in accordance with Maignon's view) a considerable proportion of the protein must be expended to supply the requisite energy. Carbohydrates, finally, take effect as savers of protein chiefly in virtue of their power to function as readily utilisable sources of energy. Thus the protein-saving effect of carbohydrates is direct, that of fats both direct and indirect. These considerations likewise explain why it is that *the best results as concerns both the utilisation of the protein in a diet and the calorie consumption of a diet are secured when the diet contains fat and carbohydrate as well as protein, and when the weight of fat is at least equal to that of the protein, whatever proportion of carbohydrate the diet may contain.*

It is or should be obvious that valid and unambiguous

results can only be expected from such experiments when the supply of food constituents is kept down to somewhere near the minimal requirements, above all as far as protein is concerned. The defect of the researches of Atwater and his collaborators is that they gave quantities of protein greatly in excess of the minimal requirements, thereby obscuring the influence of the fat upon the calorie consumption and still more its influence upon the protein consumption—for fat could be manufactured out of the surplus protein.

It used to be believed that very large quantities of protein were requisite, and those who still cling to that view will be surprised to learn that a diet containing equal quantities of fat and protein is the most economical. Amar, however, showed as long ago as 1909 that in man the best utilisation of the food is secured when the diet contained equal weights of fat and protein. The protein requirement will then be minimal, and even the fat requirement will be only a fourth or a fifth of what was formerly assumed to be necessary.

3. The importance of inorganic Constituents in Metabolism.

Before we proceed, attention must be drawn to another fact which in Germany has been strangely overlooked and has to a great extent been even directly denied. I refer to the effect of the inorganic constituents of the diet upon the utilisation of the protein it contains. The American specialists required nearly a decade to learn from their experiments that not only the total quantity of inorganic constituents, but also the quantities of the individual inorganic constituents and their mutual quantitative relationships, and in especial the relationship between anions and cations, are of decisive importance in relation to the demand for protein. But, in contradistinction to their German colleagues, the Americans did learn this in the end, and the consequences of the lesson are manifest in the incomparably better results secured by the Americans, not only in respect of the utilisation of the protein content of the experimental diets, but also in respect of the mean duration of life of the animals subjected to experiment. It is indeed strange that in the land where the law of the minimum was discovered, this law should be denied

as far as the inorganic constituents of a diet are concerned. In 1912, barely two years after myself, Osborne and Mendel [225] expressly declared that a minimum of the various inorganic constituents is essential to the maintenance of life ; a comparatively small supplement of each then suffices to ensure normal growth. A further increase of these inorganic constituents, even an immoderate increase, exercises no further influence on growth. In the next chapter this matter will be more closely considered, but it was necessary to refer to the question here because without some knowledge of it the investigations concerning the biological value of the different proteins cannot be properly appraised, and because these relationships throw light on much that would otherwise be obscure. I need merely remind the reader how long the belief prevailed that maize protein is poisonous, until at length the realisation came that the toxic symptoms which had attracted attention were merely a form of acidosis consequent on the lack of certain inorganic constituents.[451, etc.]

4. The biological Value of the various vegetable Proteins.

The most important of vegetable foods are the *cereals*. They are diffused all over the earth, wherever plant-life is possible. Many persons are of opinion that they constitute ideal foods, and Hindhede declares that wholemeal bread comprises an adequate diet without any supplement. This is by no means the case.

Rice demands consideration first, although comparatively few investigations have been undertaken concerning the biological value of rice protein. Boyd [1187] found its worth to be four-fifths that of meat protein, but his experiments are open to criticism because he was not aware of the importance of the inorganic constituents of a diet, and because his experiments were of too brief a duration. On the whole it would seem that rice protein is of a rather low grade, for Buckner, Nollau, Wilkins, and Castle [877] report, in agreement with Abderhalden,[896] that rice as the exclusive source of protein does not suffice for normal growth. In especial, the development of the genital organs is impaired, and reproduction is hindered. The insufficiency of the aggregate rice protein

would seem to be quantitative rather than qualitative. It contains all the substances requisite for tissue building, but some of them are not present in adequate amounts. If the animal can be supplied with a sufficiency of rice protein (by adding isolated protein to the rice consumed), normal development and normal growth take place. But, according to Osborne and Mendel,[736] for this result to be achieved the rice protein must comprise from 16 to 17 % of the total food. Seeing that polished rice contains only 6 % of protein, and unhulled rice no more than 4.7 %, rice as such is incompetent to promote normal development or to maintain weight. Boruttau[772] declares that ground rice (i.e. the endosperm) contains a higher percentage of protein than whole rice. There must be some error of observation here, for the experience conflicts with that of all other investigators. Otherwise there is general agreement that *in the rice grain the germ contains the highest grade and the endosperm the lowest-grade protein.*

In like manner, Osborne and Mendel[736] declare that in the case of *maize* the *embryo* alone contains protein adequate for nutrition, whereas neither the whole grain nor the flour is competent even to maintain weight in animals fed upon it. There have been numerous researches concerning the biological value of maize protein, the subject having attracted great attention because the inadequacy or toxicity of maize has been regarded as the cause of pellagra—matters to be more fully considered in the chapter on that disease. Albertoni and Tullio[337] and Sherman[1052] agree in stating that in man a nitrogenous balance cannot be maintained with maize as the only source of protein in the diet. According to Sherman, Wheeler, and Yates,[720] and according to Sherman and Winters,[746] maize protein is for human beings even worse than the already inadequate wheat protein. The inadequacy of maize protein for growing pigs has been definitely proved by Hart and McCollum,[409] Hogan,[568], McCollum, Simmonds and Pitz,[578] and Hart, Steenbock, and Letcher[900, 1143]; it does not even suffice to maintain weight in the adult pig.[578] Baglioni,[450] Hogan,[568] McCollum and Simmonds,[658] and Abderhalden[896] have proved that maize protein will not suffice to maintain growth in rats. According to Abderhalden,

the biological value of maize protein is no greater than that of the endosperm protein found in polished rice. Hart, Halpin, and Steenbock,[655] and also Nitzescu,[804] state that maize protein is inadequate even for grain-eating birds like the barndoor fowl; sooner or later the animals become emaciated and perish. Boyd [1187] likewise considers the protein of maize to be of a very poor quality, having only one-third or one-fourth of the biological value of meat protein. Maize gluten, isolated as a by-product during the preparation of maize starch, is also, according to Osborne and Mendel,[550] of extremely low biological value, although much larger quantities of it than of crude maize can be administered as food. Nevertheless, maize contains certain proteids (*maize glutenin* or *glutelin*), which are fully adequate to promote growth in animals. But the utmost amount of these in the grain is 30 %, whereas at least 50 % of maize consists of the quite inadequate zein,[217, 349, 393, 423, 1075, 1095, 1263] so that the net result of maize feeding is unsatisfactory. Of course by giving a sufficiency of the aggregate maize protein, a tolerable result could ultimately be secured, but this would be a very irrational way of feeding, seeing that two-thirds of the protein are more or less completely lacking in essential tissue-building constituents. *Zein* is especially characterised by the almost entire absence of lysin and tryptophan.[550, 613, 634] Consequently it is possible to supplement maize protein effectively by adding to the diet blood, egg albumin, edestin, cottonseed protein, casein, and, above all, lactalbumin—the two last being peculiarly rich in lysin and tryptophan. Superheating maize protein in the autoclave does not better it; on the other hand, in the case of maize as in that of cereals in general, the process of germination appears to enhance the value of the protein. Attention may here be again drawn to the fact that the maize grain, like all other seeds, is inadequate in respect both of the total quantity and the composition of its inorganic constituents.[409, 451, 568, 578, 612, 655, 900, 1143] In the case of the higher animals, the lack of calcium has a very marked effect on growth.[346] Unmistakable, too, is a grave disproportion in the relative quantities of acids and bases, and Baglioni [451] expressly states that the animals he was experimenting on (guineapigs) died of acidosis. The same

observer draws attention to a fact which seems to be connected with the foregoing, and one which I myself demonstrated ten years ago; when an animal is fed upon an inadequate protein, a retention of nitrogen may occur despite the decline in body-weight. If the maize diet be supplemented by a sufficiency of fat, etc., then (in the absence of growth) an increase in weight may occur through the deposit of fat and the retention of water in the tissues, but the retention of nitrogen is apparent merely. With the substitution of an adequate protein and the addition of a sufficiency of alkali (or even with the latter alone), there ensues a discharge of the accumulated nitrogenous and acid residues, with a resultant abrupt fall in weight. As long ago as 1909, I referred to this retention of nitrogenous residues as being the outcome of the retention of acid residues which must occur when there is a deficiency of alkalies in the food.

As regards *wheat protein*, McCollum and Davis [425] declare that 6 % in the food suffices to ensure normal growth in young rats; but these results are in sharp conflict with those of all other observers, such as Abderhalden [896] and Osborne and Mendel.[873, 1082] When working in conjunction with other collaborators (Hart,[409] and Simmonds and Pitz [579, 598]), McCollum is constrained to admit that wheat protein does not suffice to maintain growth in rats; and Johns and Finks,[1189] experimenting under very rigid conditions, come to the same conclusion. Hart and McCollum,[409] and Hart, Halpin, and Steenbock,[655] found that wheat gluten, the residue from the manufacture of wheat starch, was inadequate for growth in rats; Drummond [876] came to the same result with chickens. Hart and McCollum [409] found wheat inadequate to promote growth in pigs, and McCollum and Simmonds [691] found it inadequate to promote growth in dogs. Sherman, Wheeler, and Yates [720] found that wheaten bread made of a 74 % flour * was insufficient to maintain body-weight in human beings, and their results were fully confirmed by the investigations of Sherman and Winters.[746] According to Sherman, Wheeler, and Yates, and also according to McCollum and his collaborators, wheat protein has unquestionably a somewhat higher

* A flour resulting from a milling process in which 100 lbs. of wheat yielded 74 lbs. of flour.

biological value than maize protein, but they seem to supplement one another to some extent. A mixture of the two is still inadequate, but it gives better results than an exclusive diet of maize or wheat.

When we consider the separate proteins of wheat, we find that the relationships are much the same as with maize. According to an early (and therefore somewhat untrustworthy) investigation by Osborne and Mendel,[217] *glutenin*, one of the two chief constituents of wheat gluten, is adequate for growth, whereas *gliadin*, the other chief constituent, is quite inadequate. To convert the latter into an adequate protein, lysin must be added.[1200] But although gliadin is not competent to promote growth sufficiently,[127, 393, 1075] it is apparently competent to maintain weight.[225, 246, 423] It seems questionable, however, whether gliadin can really maintain the body's stores of protein. According to Baglioni,[393] it can bring about the maintenance of the nitrogen content of the body, and can even increase this; but just as in feeding with maize protein, so here, the increase in nitrogen content is a spurious one dependent upon the storage of residues, and is attended by an inevitable loss of weight. Since the inadequacy is mainly referable to a lack of lysin, and perhaps to some degree also to a partial lack of tryptophan, wheat protein can be efficiently supplemented by substances rich in these amino-acids, such as gelatin, meat, eggs, milk, or considerable amounts of casein, or even by the protein of the earth-nut (Arachis hypogæa). The lowest-grade protein of wheat is that in the endosperm. The protein of the bran is of much higher value, even superior to that of the germ as far as concerns richness in substances essential to the maintenance of the animal organism; on the other hand, for the purposes of growth the germ is somewhat superior to the aggregate grain, and twice as good as the endosperm protein.[772, 873, 1082] According to Boyd,[1187] the biological value of the endosperm protein is only about 39.5 % of that of meat protein.

Abderhalden[896] found in his experiments that the aggregate *rye protein* was inadequate for the maintenance of growth; it was inferior to barley protein, but certainly superior to wheat protein. Osborne and Mendel[1082] also state that rye protein is unsuited for the maintenance of growth in rats,

but according to these authors it gives better results than barley. We must leave the question undecided whether the divergency between these two authorities is to be explained by the varying conditions of the respective experiments (the Americans certainly had a better mixture of salts as a constituent of their trial diet), or by accidental differences in the specimens of grain used. As early as 1913, I was myself able to show beyond dispute [319, 614, 785, 823] that in human beings, both during growth and in adult life, the nitrogenous balance is better maintained by rye protein than by wheat protein. In the case of rye protein, too, we find that one of its constituents, *gliadin*, though fairly competent to maintain body weight,[217] is quite inadequate as a factor of growth.[225, 423] The chief lack in rye protein would seem to be lysin, but possibly tryptophan is likewise wanting, for the addition of small quantities of casein or still better of lactalbumin makes comparatively small amounts of rye protein competent to promote normal growth.[1082]

Oats play a great part in modern dietetics. It is all the more interesting, therefore, to find that the strictly scientific experiments of McCollum, Simmonds, and Pitz,[598, 625] Osborne and Mendel,[736, 1082] and Abderhalden [896] have proved clearly and incontestably that oat protein is incompetent to maintain normal growth in rats. According to Abderhalden, its biological value is less than that of rye protein. Buckner, Nollau, Wilkins, and Castle [877] found the same thing in the case of chickens. Sherman, Winters, and Phillips [939] go so far as to say that the biological value of oat protein in human nutrition is no greater than that of maize protein. In oats, as in the grains previously considered, it would seem that the proteins of the endosperm are of much lower grade than those of the whole grain.[1082] By general agreement, gelatin is an adequate supplement to oats; but whereas Osborne and Mendel [736] found that the addition of casein sufficed to make a diet of oats adequate, the experiments of McCollum in this direction gave negative results.

Barley, too, plays a notable part in modern dietetics. But in this case likewise the unexceptionable experiments of Buckner and his collaborators [877] with chickens, and those of Abderhalden [896] and Osborne and Mendel [1082] with rats,

showed that when barley protein was the sole protein in the food, growth was not maintained. This becomes explicable when we learn that *hordein*, one of the chief proteins in barley, contains no lysin, and is consequently quite inadequate.[217, 225, 423] Apparently, however, the lacking tissue builders are present in the other proteins of barley, for with a diet containing 5·4 % of isolated barley protein Steenbock, Kent, and Gross [740] find that weight can be sustained, and that when the percentage rises to 13·6 a slight growth begins. According to Osborne and Mendel,[736] normal growth takes place when the food contains from 16 to 17 % of barley protein.

According to Hogan's researches,[680] the *kapirin* of *millet* contains too little lysin and cystin to suffice even for the maintenance of body-weight.

We see, then, that none of the cereal proteins are competent to maintain the growth of the animal body,[369] and that only a few of them (rye and barley) are adequate to keep up the nitrogenous balance in the adult. Since all the proteins are different, it seems theoretically possible that in a mixture of various sorts of grain there will be a mutual compensation of deficiencies. The experiments of McCollum and Simmonds show that this compensation does to some extent occur, for mixtures of the kind have as a rule a far higher biological value than the proteins of the individual cereals used in isolation.[682, 822] Nevertheless, even the mixture of as many as eight to ten varieties of grain proves incompetent to promote perfectly normal growth, although such a mixture can ensure the maintenance of body-weight. The reason for the inadequacy is that the cereals have the common defect of containing too little lysin and cystin, and in most cases too little tryptophan as well. Furthermore, the cereals contain too low a percentage of protein, so that without isolating the proteins it is impossible on an exclusive cereal diet to ensure an adequate supply of these. In this connexion, we secure analogous results as when inadequate mixtures of amino-acids are used as experimental diets,[549] for *better effects are attained by ringing the changes on different kinds of cereal proteins than by persistent feeding with any one kind.*[896]

Pea legumin in sufficiently high doses is able to maintain body-weight,[225, 423] but is inadequate as a growth factor. The

aggregate protein of peas is, on the other hand, utterly inadequate, and according to McCollum and Simmonds its biological value is very low.[691]

In my own experiments,[319, 614, 785, 823] when *haricot beans* were used as the sole source of protein in the diet, even the approximate maintenance of body-weight was impossible. McCollum, Simmonds, and Pitz [636] also agree in forming a very low estimate of the biological value of bean protein; the replacement of the protein in an adequate diet by only 19·8 % of bean protein already suffices to upset the nitrogenous balance markedly. But a comparatively small addition of casein makes good the defects of bean protein in a marvellous manner. In later experiments, McCollum and Simmonds [658] ascertained that bean protein and maize protein are to some extent complementary, for one-third beans and two-thirds maize will determine a moderate amount of growth, which is, however, of brief duration, and is only half as extensive as the growth brought about by milk protein. Boyd [1187] therefore takes a far too favourable view of bean protein when he ascribes to it an efficiency 60 % that of meat protein.

Very remarkable is the discovery of Adkins,[1166] that the germination of beans greatly promotes the digestibility of the protein they contain; but during the drying of the beans this improved digestibility entirely disappears. Accordant is the observation made by Johns and Finks,[1094] that the addition of cystin to beans leads to no more than a trifling improvement in the value of bean protein; but that when the beans are predigested, cystin is an adequate supplement to their protein. Conflicting, however, with Adkins' observation is the further point made by Johns and Finks, that the addition of cystin renders the bean protein adequate even when the beans have been boiled for a long time and subsequently redried.

According to Osborne and Mendel,[225, 423] the *phaseolin* of beans is quite incompetent even to maintain the nitrogenous balance of the animal body.

The same authorities inform us that the *conglutin* of *lupines* is equally inadequate. Accordant with this is the fact that, in Abderhalden's experiments,[896] lupines were incompetent to maintain growth in rats.

The *vignin* of the *fodder pea*, which makes up the greater

part of the protein of that pulse, is likewise quite inadequate [225, 423]; and, speaking generally, Osborne and Mendel [665] regard the protein of pulses as of an extremely low grade. But there is no rule without exception. Two of the pulses have high-grade protein, the soy bean and the earth-nut.

Experimenting on rats, Osborne and Mendel [613] were able to secure normal growth in these animals by feeding them with *soy beans*. Elsewhere [665] they agree with Daniels and Nichols [659] in describing the soy bean as a source of high-grade protein suitable for human nutrition. Osborne and Mendel [217] were also able to secure normal growth by using *glycenin* isolated from the soy bean. Abderhalden, [896] indeed, refers to the soy bean as inadequate to promote growth in rats, but the failure here may have been due to some other cause than protein insufficiency.

Daniels and Loughlin [681] found that the aggregate protein of the *earth-nut* (Arachis hypogæa) was of great value for human nutrition. According to Johns and Finks,[1189] in the case of white rats, the replacement of 15 % of the wheaten flour in the food by earth-nut meal sufficed to secure nearly normal growth; and when 25 % of earth-nut meal was used, growth was entirely satisfactory. It follows that earth-nut protein must have twice the biological value of wheat protein. The result seems all the more remarkable seeing that *arachin* and *conarachin*, two of the chief proteins of the earth-nut, prove quite inadequate, whether given separately or in conjunction, and that they cannot be rendered adequate by the addition of cystin, tryptophan, prolin, alanin, leucin, valin, or histidin. Sure suggests that the inadequacy of these proteins may be due, not so much to the lack of this or that tissue-building constituent, as to some inner chemical peculiarities, some structural isomerism. We know of similar instances. Two of the amino-acids are readily saponifiable in one combination, but in another combination are almost unsaponifiable.

Other adequate seed proteins are found in hemp seeds, pumpkin seeds, cotton seeds, and certain nuts. Thus, Osborne and Mendel report [217] that *hemp edestin* is competent to maintain growth in rats. But its efficiency is only one half that of lactalbumin,[541] and is notably enhanced by the addition of a small quantity of cystin.[550]

According to the same authorities, the *globulin* of *pumpkin seeds* is a perfectly adequate growth factor.[225, 423]

Osborne and Mendel [493] were also able to maintain growth in rats by using *cotton seeds* as the only source of protein, and Richardson and Green [524] report a similar success. According to the last-named investigators,[654] 18 % of cottonseed meal in the food suffices to promote growth; but if the proportion be less than this, an arrest of growth occurs. They found, however,[648] that the rats' general power of resistance was increased and that the animals reproduced their kind more frequently when, in addition, 5 % of casein was given. Conformably with these results, it appears that the *globulin* of *cotton seeds*, the chief protein of these, is an adequate growth factor.[225, 423]

Nuts are often recommended as an admirable nutrient ("vegetable meat"). The recommendation is confirmed by the experiments of Cájori,[1266] who finds that (in rats) *walnuts*, *almonds*, *hazel nuts*, and *pine kernels* are competent to promote growth, development, reproduction, lactation, and the rearing of the young. Osborne and Mendel [225, 423] report that the *excelsin* of *Para nuts* is an adequate nutrient. Johns, Finks, and Paul [872] found that the *globulin* of the *cocoanut* was an adequate growth factor in rats, and that cocoanuts were almost completely sufficient as the sole source of protein in human beings. Subsequently they ascertained that by the addition of cocoanut, maize could be made an adequate food for human beings. But the *hickory nut* appears to contain only low-grade proteins, for, if growth is to be maintained on a diet of these, two-thirds of the protein must be substituted by casein.[1266]

Sugiura and Benedict,[775] feeding white rats on *bananas*, were unable to secure normal growth. When pure casein and a little yeast or extract of carrots were added to the bananas, normal growth took place and reproduction was effected, but a normal milk could not be produced on this diet. The effect of the casein does not depend upon a complementary effect upon the protein, for meat protein cannot take its place. In a later series of experiments,[980] the same observers were able to confirm the adequating influence of casein. Lewis,[968] feeding guineapigs on bananas alone,

found that the animals died in from twenty to thirty days from failure of nutrition; when oats, bran, milk, or casein, and inorganic salts, were added to the bananas, the animals throve. Anyone accustomed to the critical study of experiments of this character will derive the impression that what was wrong with the exclusive diet of bananas was not the insufficiency of the banana protein, but some other defect; perhaps there was not only a lack of calcium, but also a lack of the complettin A. Bailey Asford [129] relates that indigens convalescing from yellow fever, eat nothing but bananas, consuming from thirty to forty of these fruits daily without any supplement whatever, health and strength returning in a marvellously short time. I have myself proved that, after habituation to the strange diet, it is possible to live very well on bananas and butter, with a much lower consumption of protein than is requisite, for instance, upon a wheaten diet.

Feeding rats on *potatoes*, McCollum, Simmonds, and Parsons [777] found that growth was insufficient, even when the potatoes were supplemented with butter and salt. They estimate that the biological value of potato protein is only about half that of cereal protein. But this report conflicts sharply with the results of numerous experiments, lasting in some instances for years, made on human beings by Rubner, Thomas, Hindhede, and myself. These experiments showed that potato protein was an adequate growth factor, and also sufficed to ensure the maintenance of body-weight. In my own experiments, the biological value of potato protein was, under certain conditions, even greater than that of meat protein, and was surpassed only by that of milk protein and egg protein. The discrepancy in the respective series of observations is perhaps explicable by the inadequacy of the supply of inorganic salts in McCollum's experiments. It is possible, also, that potato protein has very different biological values for different species of animals.

McClugage and Mendel,[748] experimenting on dogs with *carrots* and with *spinach*, found that the protein of both these vegetables was quite inadequate. According to Bruntz and Spillman,[782] when rats are put upon a diet of carrots, normal growth can only be secured by the addition of casein.

It was mentioned above that conclusions as to the

biological value of a protein determined by experiments upon animals of one species are by no means necessarily applicable to animals of another species. A striking illustration of the need for caution in this respect is afforded by the varying effect of *yeast protein* in human beings and in rats. Funk and Macallum,[464] in conformity with Osborne and Mendel,[897] report that yeast (supplemented with A in the form of butter) supplies a protein which is a fully adequate growth factor in rats, and also suffices to ensure the reproduction of these animals. In human beings the result is different. Funk, this time in collaboration with Lyle and McCaskey,[567] found that for the human species the biological value of yeast protein is very low. Wintz [530] had earlier come to the same conclusion, finding that human beings could only tolerate the replacement of other proteins in the food by yeast protein up to an amount of from 20 to 25 % ; beyond that, a loss of nitrogen from the body began. Hawk, Smith, and Holder [871] likewise report that in the human species the nutritive proteins can only be substituted by yeast protein to the amount of from 10 to 30 %—to say nothing of the fact that only very small quantities of yeast can be administered to human beings without disagreeable results; 4 grammes of yeast will induce diarrhœa.

5. The biological Value of the animal Proteins.

Animal *eggs* resemble vegetable seeds in many respects, especially as regards their inorganic constituents. In the matter of the proteins, however, there must obviously be a fundamental difference, above all when animal eggs are compared with the seeds of cereals. Whereas the latter are quite incompetent to function as adequate growth factors in animals, the animal egg must perforce contain everything essential to the development of the growing animal embryo. Consequently, egg protein (as the sole source of protein) completely suffices for the needs of growing animals—rats, for instance.[425] Even in very small quantities, it can fully compensate the deficiencies of maize [393] or wheat.[873] But the remarkable thing is, that both the chief proteins of the bird's egg are adequate in this respect. Osborne and Mendel [225, 423] have proved it as regards *vitellin* ; according to Hart and

McCollum,[409] and also according to Osborne and Mendel,[349] trifling amounts of egg-yolk can render maize an adequate nutrient. This power is mainly dependent on the abundance of lysin and tryptophan in the yolk, but the cystin of the yolk must likewise play an important part. Osborne and Mendel [217, 225, 423] also confirm the adequacy of *ovalbumin*, which is competent to ensure normal growth, and can in addition make good the deficiency of maize protein,[450] although not quite so well as casein [568] (which is richer than ovalbumin in lysin and tryptophan), Maignon's observation [641, 1128] that rats, Myers and Voegtlin's observation [921] that rats, and Maignon's observation [743] that dogs, cannot live on an exclusive diet of white of egg, does not conflict with the foregoing, for the speedy death of animals in such extremely one-sided nutritive experiments is not due to protein insufficiency, but to a general lack of other nutrients, and especially of inorganic bases.

Blood protein, like egg protein, is an adequate nutrient. Comparatively small quantities of it suffice to make maize competent to sustain growth in the pig.[346] According to Hogan [568] its value largely depends on lysin and tryptophan, but also to some extent on cystin. *Blood-serum*, in especial, is so rich in cystin, that when casein (already fairly rich in cystin) is used as the source of protein in feeding dogs, a trifling addition of blood-serum to the diet leads to a distinct improvement in growth.[1183] On the other hand, Maignon [642] finds that *fibrin* is quite unsuitable as an exclusive nutrient for white rats, and that this diet soon leads to the death of the animals under experiment; but I have frequently pointed out that, since the aim of Maignon's experiments was to show that the animal organism needs other nutrients in addition to protein, and that an exclusive diet of protein is poisonous, his experiments do not really tell us anything as to the respective qualities of the proteins with which he experimented.

The rapidity of growth in mammals during the period which immediately follows birth, suffices to prove that *milk* contains an adequate protein, and indeed one of extraordinarily high nutritive value. The quantities of this protein required in the food are marvellously small McCollum and Davis [425] found that 3 % of milk protein (from cow's milk) in the food

sufficed to maintain body-weight in rats. An increase of the percentage of milk protein in the diet was attended by a proportional increase in the rate of growth, until a protein content of 8 % was reached; an increase of the percentage beyond this figure had no further influence on the rate of growth. Owing to the presence of this high-grade protein in milk, it is possible to make proteins, that are otherwise quite unsatisfactory, perfectly adequate by the addition of small quantities of milk to the diet. Thus, McCollum and his collaborators,[409, 900, 1143] feeding pigs on an exclusive diet of maize, found that the replacement of 10 % of the aggregate protein in the food by milk protein resulted in growth becoming fairly satisfactory. When the substitution amounted to 30 %, growth was perfectly normal. Sherman [1052] obtained similar results in human beings; when adults are being given an exclusive diet of wheat, maize, or oats, the replacement of only 10 % of the aggregate protein by milk protein suffices to restore normal nutritive conditions. Like observations have been made by others experimenting with wheaten diet [873] and banana diet.[968] Boyd [1187] gives the relative biological values of cow's milk protein and meat protein as 96·5 : 100; in my own experience, milk protein has a decidedly higher biological value than meat protein, both in adult and in young subjects. Edelstein and Langstein,[836] experimenting on children, found the following relative values: cow's milk casein, 73; cow's milk lactalbumin, 82; aggregate cow's milk proteins, 73; aggregate human milk proteins, 88. Fürth and Nobel [1307] likewise found human milk proteins markedly superior to cow's milk proteins; the former contain so much cystin and tryptophan that human milk, though its richness in total proteins is lower than that of cow's milk, contains more of these amino-acids than cow's milk. It must not, however, be forgotten that full milk contains in addition to proteins a number of other bodies competent (even when administered in very small quantities) to exercise a powerful influence in promoting growth. Hopkins,[202] for instance, experimenting on young rats, found that weight could not even be maintained in these animals on a diet of casein, fat, carbohydrates, and salts; but the addition of very small quantities of milk (increasing the amount of dried matter in

the diet by only 4 %) sufficed to ensure normal growth. We may suppose that the chief cause of the improvement was that the milk provided complettins, and especially A, that were previously lacking in the diet. This is striking proof that even a high-grade protein cannot sustain life in the absence of a sufficient supply of complettins.

Some earlier experiments on rats made by Osborne and Mendel [217, 225, 423] conflict with the foregoing, for casein without the special addition of complettins sufficed to bring about satisfactory development. But, in the first place, the duration of the experiments was only 30 days, and this period is too short to permit of valid conclusions being drawn; and, in the second place, there is some ground for assuming that Mendel was using casein as ordinarily manufactured, i.e. an impure casein containing fairly large amounts of A. At any rate, Lewis, Cox, and Simpson [1183] found that in dogs, when a really pure casein was used, the results confirmed Hopkins' observations on rats. Maignon's failure to secure satisfactory results by the use of casein as an exclusive diet in rats [642] and dogs [743, 941, 1128] is, as previously mentioned, explicable on grounds which have nothing to do with the biological value of the protein.

An additional proof that *casein* is a very high-grade protein is furnished by the fact that proteins otherwise inadequate may be made adequate by the addition of casein, sometimes in very small quantities. This has been demonstrated by experiments with gliadin,[349] maize,[409, 568, 578, 613, 655, 658] wheat,[579] beans,[636] carrots,[784] and oats [736]; but, as regards oats, see also [625]. According to Hogan, where maize is concerned, the addition of casein is more effective than that of white of egg. Even in the case of so high-grade a protein as cotton-seed protein, Richardson and Green [648] noted an improvement through the addition of casein, insomuch as the animals under experiment acquired a higher power of resistance, and their mortality was lessened. In the case of bananas,[775, 968, 980] too, the addition of casein to the diet was followed by marked improvement; but here a considerable part of the effect must be ascribed to the complettin A, which is always present in casein as ordinarily manufactured, and to some extent perhaps to the calcium in the casein. According

to Osborne and Mendel,[1082] however, the biological value of casein is only two-thirds that of lactalbumin.

In their earlier experiments on rats, Osborne and Mendel [217, 225, 423] found *lactalbumin* to be an especially high-grade protein. According to Emmet and Luros,[879] protein-free milk plus lactose plus 10 % of lactalbumin comprise an adequate diet, guaranteeing normal growth. But the two observers last named are mistaken in regarding the lactose in the protein-free milk as the growth factor. Doubtless the addition of carbohydrates is very important; but Osborne's researches have shown that the effective factors in protein-free milk are, over and above the complettins, chiefly the salts, and more especially the overplus of alkali in these. In a subsequent paper,[898] Emmet and Luros state that the biological value of lactalbumin is not impaired by drying or by prolonged heating, even under 15 pounds' pressure. According to Osborne and Mendel,[541] 10 parts of lactalbumin will further growth as efficiently as 15 parts of casein or 19 parts of edestin; and in various other reports,[550, 613, 877, 1082] they emphasise the superiority of lactalbumin to casein. Subsequent researches by Sure [1264] have, however, shown that the remarkably favourable results of Osborne's experiments must be in part ascribed to errors in the quality of the supplementary extracts he employed (the nitrogen content and the sulphur content of these). Exact experiment showed that chemically pure lactalbumin, though rich in lysin [349] and extraordinarily rich in tryptophan,[1307] is poor in cystin and to some extent also in tyrosin. Osborne's protein-free milk contained 0·2 % of sulphur, chiefly in the form of cystin, and also (with an aggregate nitrogen content of only 0·6 %) considerable quantities of tyrosin, whereby the lactalbumin was supplemented. Without protein-free milk, 18 % of lactalbumin in the diet produced only poor growth; whereas a food containing no more than 12 % of lactalbumin supplemented by only 0·12 % of cystin ensured normal growth. When the amount of lactalbumin in the food was reduced to 9 %, the addition of cystin did not suffice to make growth satisfactory; but a further addition of 0·6 % of tyrosin made the diet adequate in this respect. These observations throw a new light on the significance of Osborne's protein-free milk, and furnish addi-

tional evidence as to the extreme difficulty of providing unimpeachable conditions in these experiments.

The experience of the war has abundantly shown that within wide limits the composition of milk is independent of the food supply. As long as the requisite tissue-building constituents are present in the maternal organism, the mother continues to produce milk of a definite composition. This applies not only to proteins, fats, and carbohydrates, but also to complettins and inorganic salts. When the supply of any tissue-building constituent is inadequate, the quantity of the milk falls off, but its composition is unaffected. Of course this statement is true only so long as the maternal organism can provide the requisite materials, and, more especially, so long as no pathological changes have occurred in the mother's organs. The lacteal glands have no more power to synthetise amino-acids than have the other animal organs. McCollum and Simmonds [1026] expressly declare that if only one tissue-building constituent is entirely lacking, the secretion of milk is arrested. Through illness, however, and in the human species through the inheritance of morbid predisposition, the lacteal glands may be so modified that even when the diet is the best possible their secretion may be wanting, or they may furnish milk of abnormal composition.

For a very long time, *meat* has been regarded as the best source of protein, and it is universally known that for human beings meat protein is perfectly adequate.[337] According to Osborne and Mendel,[663] this is true even when the meat has been boiled and subsequently dried after expression of the juices; and Maignon [744] finds that the virtues of meat protein are unimpaired when the meat has been boiled and then extracted with alcohol and ether. The other animal organs, such as pig's liver,[663] pig's heart, or ox's heart,[702] are adequate growth factors, and so is fresh or preserved fish,[613, 690] Nevertheless, Lewis [653] finds that the value even of meat protein can be greatly enhanced by the addition of small quantities of cystin. It should, morover, be mentioned that my own experiments, as also those of Pezard [986] and Kraft,[1039] show that meat protein does not suffice even to maintain nitrogenous equilibrium unless the diet contains inorganic salts in definite quantities and proportions. This has, indeed, long been

known. If a dog be fed on meat from which the juices have been expressed, emaciation ensues after a time, toxic symptoms set in, death speedily follows, and post-mortem examination shows in the skeleton the changes characteristic of osteomalacia or osteoporosis. Carnivorous animals living in a state of nature ensure a supply of inorganic bases by drinking the blood of their victims and devouring the bones and the cartilages as well as the flesh. It also appears that wild carnivora consume at times considerable quantities of fruits, leaves, and buds; they do this especially in the autumn, whereas in the spring they live almost exclusively on animal food.

Boyd regards meat protein as the most valuable of all forms of protein,[1187] but this cannot be accepted as a positive fact as regards the protein of individual muscles, only as regards the aggregate protein of an animal body used as food. Abderhalden [452] learned this in his experiments on rats. My own researches show that the aggregate protein of eggs, that of cow's milk, and to some extent that also of potatoes, are more efficiently utilised than meat protein. In these experiments, however, the meat was given with an excess of acids. In some hitherto unpublished experiments made by Röse, in which care was taken to supply an adequate excess of alkalies, meat protein was found to have a value approximately equal to that of milk protein.

It has long been known that the biological value of *gelatin* is low. The older experiments that proved this have been confirmed by the comparatively recent work of Osborne and Mendel,[225, 423] Totani,[600] and Lecoq.[1075, 1076] Gelatin is poor in cystin, and therefore can be used to supplement proteins that are rich in cystin, or at least contain a fair quantity of that substance, such as maize protein [598] or arachin.[1253] But gelatin is rich in lysin, and therefore very moderate quantities of gelatin enable it to supplement proteins that are inadequate because they contain too little lysin (such as wheat protein and oat protein), thus converting them into adequate nutrients.[598, 625, 736]

6. The Conditions requisite for the full Efficiency of the various Kinds of Protein.

A protein is not rendered adequate merely because all the requisite amino-acids are present in it in sufficient quanti-

ties. Attention has already been drawn to the part that must be played by the mode of combination of the individual tissue-building constituents. Fischer and Abderhalden showed some time ago that alanyl-glycin can be split up by trypsin, whereas glycyl-alanin cannot be decomposed by ferments. Some such peculiarity of composition may explain why arachin is so utterly inadequate a protein, although analysis would seem to suggest that this substance ought to be of high biological value. Similar conditions must account for the very inadequate way in which zein can be utilised by rats, even when it is supplemented by the addition of the lacking tissue-building constituents, whereas zein can be efficiently utilised after preliminary hydrolysis.[600] Like considerations must explain why freshly germinated beans are better digested than dried beans [1166]; why phaseolin cannot be efficiently supplemented by cystin unless the phaseolin has first undergone a tryptic digestion or has been boiled and then redried [1094]; why a mixture of equal parts of soy bean, wheat, wheaten bran, sunflower seeds, hemp seeds, and rye meal (a mixture which is perfectly adequate in the crude state), proves conspicuously inadequate after it has been made into a paste with water and then baked.[877] In such cases, therefore, the student of nutrition must have an eye to these details.

It is likewise necessary to point out that (in accordance with the law of the minimum) *when there is a lack of complettin, even the highest-grade albumin will be incompetent to promote satisfactory development.*[1039, 1264] There is no means of ascertaining the requirements of the organism as regards any particular constituent, unless in respect of every other condition the diet is all that can be desired.[294, 664]

On the other hand, in experiments on nutrition, it would be a mistake to supply any constituent of the diet in quantities exceeding the optimal amount. There are two objections; first of all, this needlessly overloads the organism; and, secondly, it increases the minimal requirement of other constituents. *The diet must contain a sufficiency of all necessary ingredients, but there must be no notable excess of any.* For example, in experiments upon the effects of complettins, it would be a mistake to give an excess of protein in order to

ensure that the results shall not be invalidated by protein deficiency. Inasmuch, however, as the biological value of the different proteins varies enormously, and the minimal requirement of protein will vary in accordance with the nature of the supply,[836, 837, 1067, 1288] in such experiments the most sedulous attention must be paid to the biological value of the proteins supplied in the food. Of course the best way is to have a preliminary series of control experiments in order to ascertain the quantities of proteins that are necessary, or the nature and amount of the requisite supplements.

The investigator must also bear in mind that *the protein requirements vary at different ages*. In adult animals and human beings, it suffices to give quantities of protein competent to maintain the body-weight throughout experiments of considerable duration. During growth, however, very different conditions prevail.[225, 423, 425] At this time of life, besides the quantity of protein needed to maintain body-weight, there must be given enough protein to ensure that development and growth shall proceed at least as fast as if the animal were free to choose its own food from an unrestricted supply. The first requisite, then, is a thorough knowledge of the normal development of the experimental animal under the most favourable conditions, and this presupposes abundant statistics, such as Robertson and Ray [483, 484] have supplied in exemplary fashion in the case of the white rat Next, there must be an increase in the protein supply sufficient to provide for the increase in the tissues. The requisite increase, again, varies at different periods of growth, and may at times be very large. In my own experiments,[319] I found that the protein requirement of the growing youth exceeded that of the adult male by from 50 to 80 % ; Benedict,[993] Holt,[1117] and others record similar results. In young persons from 13 to 19, during the holidays, the protein requirement is almost twice as great as that of adults.

In the earlier studies we are usually informed that the basic turnover is lower in women than in men. To-day we know this assumption to be untenable. At times, owing to the catamenial losses, a woman needs more than a man, of equal weight and doing the same amount of work, to maintain bodily equilibrium. It will readily be understood that the

minimal requirement will rise considerably when reproduction and the rearing of offspring have to be provided for in addition to self-maintenance.[995, 1052] During the present chapter we have repeatedly learned that a protein may be adequate for the maintenance of body-weight, but inadequate for the needs of reproduction and rearing.

As regards human beings, as early as 1913 I pointed out that, when the conditions are in other respects optimal, the amount of protein requisite to maintain body-weight is far smaller than has hitherto been supposed. American investigators have confirmed this contention when their experiments have been carefully designed. Boyd,[1187] for instance, giving meat as the source of protein, estimates the minimal daily amount of protein requisite to maintain body-weight at 30 grammes; whereas in my own experiments, under more accurately adjusted conditions, the requirement was 26 grammes of meat protein; and Röse, providing a better supply of alkalies, found the meat protein minimum to be 24 grammes. Sherman,[1052] in a critique of all previously published results, and after conscientiously making allowance for all accessory factors bearing on the various experiments, came to the conclusion that the protein requirement in a person weighing 70 kilogrammes averaged 40·6 grammes (ranging from 30 grammes to 50 grammes); being 0·58 grammes of protein per kilogramme of body-weight. In another communication,[995] this observer declares that from 35 to 45 grammes of protein daily (0·5 to 0·6 grammes per kilogramme of body-weight) are quite sufficient to maintain weight in a healthy human being weighing 70 kilogrammes, even though the proteins be not carefully selected, nor of a specially high grade. A supply equivalent to 1 gramme of protein per kilogramme of body-weight, when a mixed diet is taken (i.e. when there is no careful selection of particular nutrients), provides a margin of safety of from 50 to 100 %. For growth and reproduction, larger quantities are, of course, requisite, and it is also desirable in that case that the proteins should be of high biological value.

CHAPTER THREE

THE IMPORTANCE OF INORGANIC SUBSTANCES.

1. The Supply of a Sufficiency of nutritive Salts.

In German scientific circles, the term "nutritive salt" is in bad odour; its mere presence in a scientific essay suffices to discredit the work. Nor was this attitude entirely unfounded, at one time. The importance of the proteins and of the supply of energy was so conspicuous to all students of human dietetics, that the importance of inorganic salts to nutrition was entirely overlooked by scientific observers. All the more, therefore, did these salts win the favour of the laity and of quack-doctors; they were regarded as a panacea, recommended indiscriminately for the relief of all troubles, from heartburn to cancer and consumption, so that nutritive salt preparations sprouted in the market like mushrooms after rain. We may question, however, whether the medical profession was well advised when, in the hope of checking the evil, it tabooed all reference to the problem. Beyond question the wiser course would have been to ask what fire there was behind so much smoke. The result of the taboo was that as recently as ten years ago not a single complete and accurate analysis had been made of the inorganic constituents of any organ in man or the lower animals, of any of the bodily juices, or of any of the excretions. Quite an outcry was raised when at that date I ventured to maintain as much, and it is but a melancholy consolation that last year the fact was fully confirmed by the Experimental Stations Office in the United States. Characteristic of the situation is it that (with the exception of Röse's fundamental investigations concerning the calcium requirement of human beings, which

were supplemented by the work of Emmerich and Loew) all the research in this field was undertaken by students of animal physiology, whereas specialists in human medicine held aloof.

In excuse it may be mentioned that even when physicians did occupy themselves with the problem (as Heinrich Lahmann, for instance, endeavoured to do), no satisfactory results were obtained. Trustworthy data could not possibly be provided by the analytical methods then available, in experimental stations and experimental laboratories, for the inorganic constituents of food and the organs of the body. More precise methods of analysis had to be elaborated before such researches offered any hope of success.

Naturally, therefore, the first studies of the complettins were all affected for the worse by our ignorance of these matters. Such skilful experimenters as Osborne and Mendel, or in Germany Röhmann, were entitled to congratulate themselves when the animals under observation (rats) could be kept alive 80 days on an artificial diet. Even in Kochmann's and Fingerling's researches, this ignorance had a very disturbing effect, and largely obscured the results. Röhmann tried numerous mixtures of inorganic salts before he at length secured a fairly satisfactory outcome.[42, 72] The successful mixture is of historic interest, and its composition therefore worth recording here. It consisted of: tricalcium phosphate, 10 grammes; bipotassium phosphate, 37 g.; sodium chloride, 20 g.; sodium citrate, 8 g.; calcium lactate, 8 g.; iron citrate, 2 g. The investigator who was able empirically, out of numerous failures, to arrive at such a mixture, must have been sagacious, and must have had the benefit of wide experience. It is especially significant that the mixture contains an excess of bases, this excess amounting to 130·2 milligramme-equivalents in every 100 grammes of the mixture of salts, thus fulfilling what I have from the first regarded as an essential requirement of a properly arranged diet. Nevertheless, the mixture has grave faults. It is overloaded with phosphates and sodium chloride, and the ratio between potassium and sodium is only 0·64 to 1 instead of about 3 to 1. The ratio of calcium to magnesium is likewise far too low, being only 0·67 to 1 instead of 5—7 to 1. Further-

more, the composition of Röhmann's mixture of salts shares the defects of almost all the mixtures hitherto recorded: it is completely lacking in manganese, zinc, and soluble silicates.

Osborne and Mendel[150] have shown that Röhmann's mixture is far from perfect. Their successes with a milk diet led them to use protein-free milk as the provider of inorganic salts. The milk having been acidulated with hydrochloric acid until all the protein had been precipitated, was then warmed and filtered, the clear filtrate being subsequently neutralised with soda solution. In 100 grammes of dry substance, this preparation contains: Ca, 1·92; Mg, 0·20; Na, 2·18; K, 2·82; PO_4, 3·52; Cl, 4·44; SO_4, 0·27. Hence 100 grammes of inorganic substances contain 934·2 milligramme-equivalents. In respect of excess of bases, as regards the ratio of potassium to sodium (1·52 to 1), and as regards the ratio of calcium to magnesium (5·9 to 1), there has been great improvement. The method of analysis was, however, faulty. This is manifest at the first glance, for 100 grammes of the preparation gave only 15·02 g. of "ash," whereas the enumeration of the ions gives 15·35 g. Furthermore, no determination was made of the other inorganic constituents of the milk: iron, manganese, zinc, aluminium, and silicic acid. This is a typical instance of the defects of the analytical methods hitherto employed.

In view of Osborne and Mendel's results, it is interesting to recall that Heinrich Lahmann made the *ash* of cow's milk the basis of his speculations concerning the inorganic salts required by human beings, and that he was overwhelmed with derision, mockery, and vituperation by his fellow-countrymen for his pioneer attempt to solve the problem. Instead of following up the line of research indicated by Lahmann, people made fun of him for "proposing to nourish adults as if they were infants-in-arms." The history of science shows many strange aberrations!

The chief defect attributable to this first attempt is that in the work of Osborne and Mendel, and especially in that of Lahmann, the excess of bases in the milk was greatly underestimated. In both cases alike, and more particularly in the analyses taken by Lahmann from the literature of the

subject, the analytical technique was faulty, so that the quantity of alkalies was stated at too low a figure, and the presence of iron, manganese, aluminium, zinc, and perhaps copper, was overlooked. Furthermore, there was a theoretical error in Lahmann's assumption which escaped all his opponents, though some of them were on the verge of detecting it. Natural milk contains acid-rich proteins, and unless these proteins are fully utilised by the body (as they are in the suckling undergoing normal growth) the total surplus of bases in the milk is not placed at the disposal of the organism —as it was in the American experiments with protein—free milk. If the bodily requirement of protein is less than the amount of protein supplied in the food, then the acids in the surplus protein will neutralise the excess of alkalies in the protein-free milk. In actual fact, it appeared in my own experiments [319] that when only so much milk was given as would satisfy the bodily requirement of protein, the excess of alkalies in the cow's milk did not suffice either for the growing youth or for the adult human being. In like manner, Lyman and Raymund,[962] experimenting on rabbits (which are very sensitive to acids), found that on a diet of cow's milk the animals perished of acidosis; but when sodium citrate was added to the food, the acidosis disappeared and the urine contained less ammonia; even when ammonium lactate was given, instead of sodium citrate, the acidosis disappeared, and the urinary ammonia was reduced although an ammonium salt was being administered.

Following in Lahmann's footsteps, McCollum used the ash of cow's milk for the supply of the necessary salts, but had to give very large quantities in order to secure tolerably good results. Subsequently, instead of cow's milk ash, he used an artificial mixture of salts, which was somewhat better, but still contained too little alkali, and also had the same defects as Osborne and Mendel's mixture. Moreover, the experiments of McCollum and his collaborators were too brief, and were therefore less satisfactory than those of Osborne's school.

In later experiments, Osborne used a purely artificial mixture of salts, for too many sources of error were introduced by the presence of organic substances in the protein-free milk. This mixture had additional merits; and since it

appears to be the best yet employed, its composition may be given: calcium carbonate, 134·8; magnesium carbonate, 24·2; sodium carbonate (dried), 34·2; potassium carbonate, 141·3; H_3PO_4, 103·2; HCl, 53·4; H_2SO_4, 9·2; citric acid (crystals), 111·1; iron citrate (crystals), 6·34; potassium iodide, 0·02; manganese sulphate, 0·079; sodium fluoride, 0·248; potash alum, 0·0245. Here the ratio of sodium to potassium has been improved, being now 3·2 to 1; and the new mixture contains iron, manganese, aluminium, iodine, and fluorine. The ratio of calcium to magnesium is less favourable than it was in the earlier mixture, but this is a minor defect in view of the other improvements; and although the excess of alkali is reduced to about a third of what was formerly present, a larger dosage with the mixture of salts will to some extent compensate the deficiency. Two additional errors must be mentioned: there is far too little manganese (the quantity might well be multiplied by a hundred); and silicic acid is not represented. If these defects were remedied, if the quantity of magnesium were somewhat reduced, and the proportion of phosphoric acid lowered by a third, I should consider the mixture thoroughly abreast of modern knowledge of the bodily requirements of inorganic constituents.

None the less, the biological value of this nutritive mixture may at times be improved by certain modifications, as by the addition of bases that are inadequately represented in a natural diet—and especially when the addition changes an excess of acid in the food into an excess of alkali. Thus Hart, Halpin, and McCollum,[612] feeding chickens on maize, Hogan,[634] feeding rats on maize, and Daniels and Nichols,[659] feeding rats on soy beans, were able to ensure adequate growth by the simple addition of potassium carbonate. As a rule, however, seeds of various kinds must be supplemented by the further addition of sodium and calcium [645, 682, 691, 739]; and we have similar reports regarding potatoes,[777] carrots,[784] and bananas.[968] Even milk is well known to be adequate in respect of inorganic constituents only for the earliest period of life; but for adults it is rendered adequate by the addition of a little iron. In my own experience, however, as far as adults are concerned, the richness of milk in protein makes the excess of alkali in this food inadequate.

In particular cases, special factors come into play to modify the requirement for inorganic constituents. Especially interesting in this connexion is the fact that cottonseed meal manifestly contains a toxic substance which makes it quite unsuitable as an exclusive diet, but that this toxic substance is rendered harmless by the addition of inorganic iron salts to the food.[662]

2. The Importance of individual inorganic Substances.

There is still a great gap in our knowledge of the part played by inorganic substances in metabolism and in animal physiology generally. In addition to the inorganic substances mentioned in the previous section, there are certain others, present more or less regularly but in far smaller quantities, whose importance still remains obscure. Any investigator who would bestir himself to throw light on the matter, would certainly do good service. Some substances, such as the rarer metals occasionally met with in various organs, may be excluded from consideration as of no importance. But in the case of any substance whose presence in the body is invariable, two conflicting interpretations of its presence are possible. We may be concerned with an element universally present in nature, though in very small quantities; and we may suppose that traces of this element are inevitably introduced into the body day by day with drinking water or with food, and especially with vegetable food. Not until a certain accumulation of such an element has occurred within the body will the excretory organs take note of it and proceed to eliminate it from the system. But the problem that arises is, whether such a substance (though present only in the minutest traces) is nevertheless essential to life and wellbeing; or whether it is merely a passenger, an ingredient whose entry is unavoidable but quite unimportant—unless, indeed, it prove harmful to the organism when the quantity exceeds a certain minimum. Of especial importance is this question as regards zinc, copper, and arsenic, which are always present, and even in notable quantities. Although zinc is found in comparatively large quantities, the demonstration that it has positive biological importance would be a new and sur-

prising fact; but we have more inclination to suppose that copper and arsenic may exert a stimulating influence that is of moment to life.

Although a mixture of inorganic salts containing no soluble silicates, and perhaps no zinc, copper, or arsenic, may give satisfactory results in dietetic experiments, we must not infer that the substances named are not essential to life. Even in the most carefully purified diet, traces of them may be present as impurities of the organic constituents. If they have not hitherto been detected, the failure to find them may perhaps be accounted for, not by their absence, but by the inadequacy of the analytical technique. Soluble silicates, in especial, are often present where least suspected. It must, moreover, be remembered that the substances in question are present in the body in very minute quantities, which may gradually accumulate out of almost infinitesimal supplies in the food.

Earlier physiologists would have flatly denied that such homeopathic doses of any substance could possibly be of vital importance. To-day we have learned caution, since we have, for example, in iodine a substance minute traces of which can exercise an extremely potent influence upon living tissue. Furthermore, the study of the complettins has brought quite a number of similar instances to light. Strictly scientific investigation can alone justify a decision upon such matters; we must not jump to conclusions under the spur of mere feeling. The rejection of possibilities without due examination has already wrought sufficient havoc both in biology and in medicine.

Aron and Gralka [1386] have recently recorded the composition of a mixture of salts used by Aron in dietetic experiments. The mixture is a good one in two respects: the excess of alkali amounts to 743·1 milligramme equivalents in 100 grammes of inorganic ions; and the ratio between calcium and magnesium is 4·8 to 1. In other respects, however, Aron's mixture marks a step backward, for the ratio of potassium to sodium is only 0·8 to 1; and the mixture contains neither manganese, aluminium (zinc), iodine, fluorine, nor silicic acid. The reader may be inclined to think that I am overstressing these criticisms. We must, however, perpetually bear in mind that the law of the minimum is fully applicable

to all the substances named. Should any one of them be lacking, a perfectly normal development is impossible. Inasmuch, moreover, as inorganic substances enter into important reciprocal relationships (predominantly during excretion, but also during the synthesis of organic substances), we are concerned with a qualitative as well as with a quantitative minimum. When, for example, a substance is being given in quantities that are adequate per se, but another substance is being also given that antagonises the former, the quantity of this is thereby rendered inadequate.

At an early stage of the investigation, this was recognised by Röhmann,[42, 72] and also by Osborne and Mendel.[150] In another paper,[225] the last-named insist that for regular development something more is essential than a minimum of the inorganic constituents of a diet; if development is to be normal, these mineral constituents must likewise be present in the proper ratios one to another. Elsewhere,[1224] Osborne has recently insisted that our interest in the problem of the complettins must not lead us into the old mistake of forgetting other important factors. He says that the need for the proper supply of inorganic constituents must on no account be overlooked, and he draws particular attention to the deficiency of calcium and iron in many common foodstuffs. Lecoq [1047] also insists that the quality of nutrition is not solely determined by the amount and nature of protein, complettins, and the supply of energy, but that inorganic constituents must be provided in sufficient quantity and in the proper mutual proportions. Scala [1317] reproaches physiologists who are experimenting as to the causation of deficiency diseases with uncritically referring all the manifestations to the account of the complettins, and with forgetting that the organic extracts they use in their experiments contain in addition comparatively large quantities of inorganic substances which likewise exercise a powerful influence. Above all we have to remember that when an extract is made from uncoagulated material, chiefly the bases pass into solution; whereas when the extract is made from material in which the protein has been coagulated by heat, acids predominate in the solution. This fact may in part explain the reported behaviour of the thermolabile complettins.

Reference may be made to the researches of Forbes, Halverson, and Schulz [1188] as examples of the importance of the proper choice of a salt. It is well known that pigs fed on an exclusive grain diet do not develop properly. Since the animals ultimately become affected with osteoporosis, the failure of development has been referred to the deficiency of calcium in the food. If, however, prepared bone ash (the chief ingredient of which is bicalcium phosphate—a third-part acid salt) be added to the food, not merely does this fail to induce improvement, but it actually makes the disease worse. On the other hand, calcium carbonate, which functions in the animal organism as an alkali, completely cures the trouble. The main cause of the disorder, and perhaps the sole cause, is, in fact, the acidosis evoked by the food, and not a deficiency of calcium, for the bicalcium phosphate reduces the alkaline reserve of the blood by 15 %, whereas an equal quantity of calcium carbonate increases the alkaline reserve by 10 %.

3. The Importance of an Excess of alkaline Substances.

American investigators have recently drawn attention to the need, in this matter of the inorganic ingredients in the food supply, that we should distinguish on principle between seeds and leaves.[636, 658] Leaves contain an excess of inorganic bases, whereas seeds contain an excess of inorganic acid-formers.[8, 407, 507, 524, 578, 612, 636, 645, 658, 659, 681, 682, 691, 720, 740, 900, 956] They have overlooked the fact that in my tables [306, etc.], I found it possible to divide all foodstuffs into two classes in accordance with this principle : excess of acid is characteristic of all animal organs and every kind of muscular tissue, and of fats, eggs, seeds, and buds ; whereas roots and tubers, stalks and leaves (" vegetables "), bulbs and fruits, are characterised by excess of alkali—cranberries being a notable exception. It is therefore always possible, without monotony, to choose a diet containing an excess of alkali. We need merely mix the acid and the alkaline nutriments in due proportions.

Of course this rule must not be applied too rigidly. For instance, the study of *Lecksucht* [variously known in English as " the lick," " pica," " wool-eating," etc.] in domesticated

animals has shown that grasses, etc., which are ordinarily rich in alkalies may in an unfavourable soil (such as moorland deficient in lime and potassium) acquire an acid reaction, and that animals which feed upon such pasture become seriously ill. In like manner, cultivated plants, when too exclusively manured with nitrogenous fertilisers, and above all when treated with liquid manure poor in alkalies (Berg [306], etc.; Liechti and Truninger,[282]; Liechti and Ritter [1333]) or with ammonium sulphate, exhibit deficient alkalinity, and may become positively acid.

No doubt the same rule applies to animals as to plants: Nature has once for all prescribed an optimum composition, which cannot be improved upon though it can be changed for the worse. In the previous chapter, stress was laid upon the observation that, while the composition of the maternal diet certainly has a notable influence upon the quantity of milk produced by a nursing mother, the quality of the milk, i.e. the amount of organic nutrients it contains and the composition of these, is substantially independent of the mother's diet—so long as milk is secreted at all and the mammary glands remain healthy. These glands exhibit great energy in extracting the requisite materials from the maternal organism, and the source of milk does not dry up so long as the materials for the manufacture of the secretion are forthcoming. Röse [69, 70] has proved this also in the case of the inorganic constituents of the milk, especially as regards calcium in goat's milk. McCollum and Simmonds [1026] likewise draw special attention to the fact.

When, however, noxious influences are at work for a very long time, they ultimately affect even the lacteal secretion. Hess, Unger, and Supple [1332] found that when cows were stall-fed for a considerable period upon fodder poor in calcium, the aggregate ash in the milk was somewhat diminished; the reduction was especially marked in calcium and phosphorus, but the sulphur was somewhat increased. This change is parallel to that which occurs in plants when an acid grass is produced in a soil rich in nitrogen but poor in inorganic constituents generally. The question certainly arises (and it is one which the experiments leave entirely unanswered), whether such protracted deficiency of inorganic

nutrients may not directly injure the lacteal glands, so that these can no longer be regarded as normal. Thus Röse [69, 70] found, in contrast with the data furnished by two years' experiments on goats, that in women the capacity for lactation runs fairly parallel with the calcium content of the drinking water; in places where several years earlier a supply of soft water had been inaugurated, he ascertained that there had been a notable decline in the period of lactation.

Let me take this opportunity of reiterating the warning that, as regards the real need of the animal organism for any particular substance, brief experiments are absolutely valueless. Experimental animals may seem perfectly healthy, may develop and reproduce their kind, and only in the third or fourth generation do degenerative symptoms make their appearance as the outcome of deficiency of some inorganic nutrient—control experiments showing that animals under the same conditions, except that they are adequately provided with this nutrient, remain quite free from these symptoms. From a communication made to me verbally by Urbeanu I learn that he saw barndoor fowls, provided with what seemed a bare sufficiency of calcium, develop for three generations in a way that appeared perfectly normal; but the birds of the third generation were sterile because their eggs had no yolks. Control birds were still entirely normal in the fifth generation.

That is why the embryo has so vigorous a tendency to maintain the calcium content of its own organism at all costs. It is a familiar fact that during pregnancy a woman inadequately supplied with lime salts is apt to lose her teeth; and, in bad cases of deficiency, she may even become affected with osteomalacia. According to the researches of L. Zuntz,[861] the calcium content of foetal rats remains normal when the parent rats are inadequately supplied with lime salts; calcium deficiency in the food did not influence the calcium content of the offspring of these animals unless the noxious influence had been persistently at work long before conception. In such instances, however, the entire development of the offspring was seriously impaired.

It seems expedient to remind the reader that the preparation of the food may also influence its richness in inorganic constitu-

ents. I have already pointed out that, according to French investigators, when milk is boiled the complex calcium-magnesium carbono-phosphate it contains is decomposed, and is precipitated in an insoluble form; and McCollum and Parsons [1300] tell us that the precipitated salts cling to the walls of the container. Thereby the quality of the food is doubly impaired. In the first place a natural inorganic product, directly assimilable and immediately available for bony growth, is metamorphosed into a form hard to assimilate, and is in part actually eliminated from the milk. In the second place, and simultaneously, the excess of alkali in the milk (already low) is gravely reduced. When, after boiling vegetables, the water in which they have been boiled is poured away, the result is similar, inasmuch as the more soluble bases are removed, so that even vegetables which were primarily rich in bases will exhibit an excess of acid after such treatment (Cf. Berg [141, 333, 1516].) Finally, the medicinal administration of acids, whether aromatic acids of organic composition such as salicylic acid and benzoic acid or inorganic acids such as boric acid and sulphuric acid, leads to a dangerous loss of bases, inasmuch as these acids can only be eliminated from the body after combining with the inorganic alkalies it contains.

In the previous chapter we learned that an excess of bases in the food is desirable were it only to ensure optimal conditions for the utilisation of the proteins in the diet, and to reduce the liability to the formation of noxious products of metabolism. I should like to refer here to the experiments of Abderhalden,[452] who found that alkalinisation of the food with sodium acetate brought about a more efficient utilisation of the protein in the food; and also to the observation of Benedict and Roth [420] who noticed that in vegetarians (human) the basic turnover was less than in persons on a mixed diet.

It has long been known that when herbivora, and still more when rodents, are fed exclusively on grain, acidosis rapidly ensues. In rabbits on a maize diet, for instance, the acid urine contains far more phosphorus than is being introduced in the food. Simultaneously the ammonia content of the urine is greatly increased, but Underhill [565, 566] states that

in spite of this the animals' nitrogenous balance is maintained. The only possible explanation is that under the influence of the acids a vigorous production of ammonia ensues; this being insufficient to neutralise the acids, the body, in its need for bases, is compelled to turn to the osseous system, the last alkaline reserve of the organism. Another familiar fact is that an inadequate supply of food, or absolute starvation, both of which lead to an enforced disintegration of the body's own protein, give rise in herbivora to the same phenomenon that ensues upon an exclusive meat diet or grain diet, namely acidosis, with alkali impoverishment of the body, and kreatinuria. A remarkable fact is that, during the acidosis, even in the meat-eater, hypoglycæmia ensues, exactly as in the case of direct poisoning, as for example by hydrazin sulphate. An injection of sodium hydrate will promptly render the urine alkaline once more and will simultaneously put an end to the kreatinuria. Inasmuch as in herbivora a grain diet also induces acidosis, this disorder cannot, as is often maintained, be the outcome of carbohydrate deficiency.

Rats, again, can only endure an exclusive grain diet for a short period, speedily succumbing on such a regimen. An abundant addition of protein to the grain does not help them. Hogan, however, tells us that an addition of alkalies preserves their life and has a marvellous effect in furthering growth.

Hart, Miller, and McCollum,[515] and Abderhalden and Ewald [683] have shown that an excess of acid in the food must often play a part in the causation of the avitaminoses; in the later chapters of this book the fact will again and again force itself on our attention. Peckham [1310] stresses the relationships and reciprocal actions of inorganic nutrients and complettins. In this connexion we may allude to Aulde's observation [1259] that when there is either a lack of calcium or an excess of acid in the food, the complettin A is void of effect; and that conversely the assimilation of calcium and the full development of the anti-inflammatory properties of this base are only possible in the presence of A.

According to Steenbock, Nelson, and Hart,[410] the direct addition of acid to the food always causes an increased excretion of ammonia in the urine and a decreased excretion of urea In omnivora and carnivora this decline in urea is said

to take place by way of compensation, and these authors therefore assume that in such animals an abnormal disintegration of the protein in the food already takes place in the intestine, accompanied with the formation of ammonia, and that the body protein remains intact. In herbivora, on the other hand, it is supposed that the taking of acids with the food involves also the disintegration of the body protein, so that the formation of ammonia is increased to a greater extent than the formation of urea is diminished, and the nitrogenous balance becomes negative. In criticism of these experiments I must point out that the diet was not one in which the ingestion of nitrogen had been reduced to a minimum, and that their duration was too brief. Had it been otherwise I am sure that the observers would have found, as Röse and I found, that in human beings, and in omnivora and carnivora, direct losses of nitrogen occur in such conditions.

We have to remember that dogs and pigs, as normally fed, receive far more protein than is essential for their minimal bodily requirements, and that thereby a quantity of ammonia competent to neutralise the acids added to the food is liberated within the system. If no more protein than the indispensable minimum had been given, and if the requisite supply of additional energy had been provided by giving fats and carbohydrates, the consequences of the addition of acids to the food would have been promptly manifest in these animals too.

Hopkins [1055] points out that under certain conditions acidosis can be partially relieved by an abundant supply of protein, thanks to the extensive formation of ammonia out of the surplus protein. But we must not go too far with this supply of protein, for Maignon has shown again and again that an exclusive protein diet is positively toxic even in a carnivore. Whipple and van Slyke [729] had similar results in their experiments. Feeding on large quantities of meat causes symptoms of acute poisoning resembling those occasioned by an injection of albumose, attended by similar conditions in the blood—those characteristic of tissue destruction. In collaboration with Birkner I have shown [294] that this decomposition of the tissues must arise from the changes in the bodily juices determined by an excessive production of ammonia.

4. Acidosis.

Given certain conditions, it does not take much to induce acidosis. Bossert [1014] points out that in children with a predisposition to spasmodic affections (and only in these) the mere addition of one egg to the daily diet will give rise to oedema with retention of nitrogen and inorganic constituents, and sometimes to the occurrence of carpopedal spasms. When the egg is withheld, normal conditions promptly return. Manifestly in such cases the existence of an affection of the nervous system explains why the acidosis has so powerful an influence; and we must invoke the same explanation to account for various observations that, in cases of severe diabetes, epileptiform convulsions occurred as soon as acidosis set in.[1044, 1174, 1175] (Cf. also Elias [676].) Shaw [1182] likewise found that when certain nerve degenerations were present, acidosis arose more readily and had a more powerful effect —as for instance in epilepsy, severe malaria, chronic melancholia, and chronic alcoholism. In conjunction with the acidosis, "epileptic" paroxysms occurred, especially during the night, when the reaction of the blood is physiologically less strongly alkaline than during the day. At the same time, the blood exhibits a marked excess of hydrogen ions. In such cases, an increase of protein in the food leads to an increase in the frequency of the paroxysms, whereas the administration of alkalies reduces their frequency. At the post-mortem examination in cases of acidosis, there was found cloudy swelling of the pia-arachnoid, such as is commonly observed after death from poisoning by the mineral acids.

Although in various skin diseases (psoriasis, acne, eczema, and seborrhoic dermatitis) the acidity of the blood and the urine is sometimes found to be increased. Sweitzer and Michelson [1104] state that this is not invariably so, and they therefore regard acidosis as at most an accessory factor of these diseases.

As a general rule, we have to reckon only with the inorganic acid-formers as the originators of acidosis. In my published works, however, I have repeatedly insisted that when an excess of organic acids is taken, so that the organism

is unable to effect their complete combustion into carbonic acid and water, they must have precisely the same effect as the inorganic acids, seeing that they too must be neutralised by inorganic bases before they can be excreted. Thus in human beings the immoderate ingestion of dilute acetic acid (table vinegar) or citric acid (lemon juice) may lead to typical symptoms of acid poisoning, as may unfortunately be often seen in persons who are undergoing the popular "lemon cure." Obviously, too, an immoderate supply of carbohydrates may arouse like manifestations, if these food-stuffs undergo acid fermentation in the bowel. Indeed Barr [1055] regards some of the symptoms of beriberi and of experimental polyneuritis as consequences of an acid poisoning due to the intestinal fermentation of the carbohydrates that are too liberally supplied in the food. It is far from improbable that the so-called "Mehlnährschaden" of infants-in-arms is in part dependent on similar causes.* This explains why Dreifus [1065] found that in the rabbit the rectal administration of dilute organic acids in quantities that were tolerated by mouth, proved fatal. The acids were quickly and directly absorbed into the blood through the mucous membrane of the large intestine, whereas when taken by mouth they could enter the blood only through the devious route of the lymphatic system, and could on the way be neutralised—partially at least.

There are also numerous reports to the effect that the abundant ingestion of fat may lead to acidosis. This is well known to occur in diabetics, whose powers of oxidation are in any case impaired. We must, however, bear in mind that

* Detailed accounts of the syndromes known in Germany as Mehlnährschaden and Milchnährschaden will be found below, p. 295 and p. 297. They are nutritive disorders in bottle-fed infants, respectively due to feeding with cereal food and with diluted (usually pasteurised) cow's milk. It neither becomes us nor behoves us as translators to rush in where British experts fear to tread. The leading British authorities on the diseases of children have failed to differentiate what the Germans call Mehlnährschaden and Milchnährschaden from the generality of cases of infantile marasmus. That is why we have to use the German names in the text. The lack of suitable English terms dates from ten years back. In 1913, Casimir Funk, at that time director of the physiologico-chemical laboratory of the Cancer Hospital Research Institute in London, wrote: "In English pediatric literature, the concept Mehlnährschaden is quite unknown, the disorder being usually included under the heading atrophy. . . . Milchnährschaden certainly belongs to the same category of nutritive disorders" (*Die Vitamine*, Bergmann, Wiesbaden, 1914).—TRANSLATORS' NOTE.

as regards fats there is a difference in the mechanism by which acidosis can be produced. The splitting up of fats, with a consequent liberation of fatty acids, takes place in the intestine. Since, as far as we know, free fatty acids cannot be absorbed by the intestinal epithelium, the neutralisation of these acids must be effected within the intestine itself at the cost of the alkalies in the bile. Of course this, too, leads to alkali impoverishment. The only difference is in the place where the loss of alkalies occurs; the net result is the same.

Uhlmann [1216] reports instances of obstinate acidosis in severe cases of diabetes, in which the regulation of the carbohydrate supply no longer leads to any improvement, but a reduction in the amount of fat ingested is followed by a reduction in the excretion of acetone. In like manner, Bierry and Portier [732] and also Dubois [733] report that in rats the weight can be maintained by a diet of coagulated protein, fat, carbohydrates, and salts, in definite proportions; but that when the proportion of fat is unduly increased, acidosis ensues, leading to acetonuria and emaciation.

In view of the observations made by all other physiologists, it is rather presumptuous of Bayliss [1236] to assure his readers that the notions of acidosis and alkalosis are apriori untenable and to declare that other explanations must be found for the manifestations classed under these names, seeing that as long as the organism is alive it is perfectly able to compensate such noxious influences!

Confusions of this kind arise mainly from a lack of precision in the definition of acidosis. This, in turn, results from the mixing up of two ideas which to some extent are entirely distinct, the confusion having taken place during the early enthusiasm of the "ionic days" when investigators were full of the joy of creation and discovery. In experiments with pure salts it appeared that acidity or alkalinity corresponded with the H or OH concentration, and "reaction" incontinently identified with "ionic concentration." In reality, we chemists understand something more by reaction, namely the power of neutralising an acid or a base; and in organic chemistry numerous substances are encountered which unquestionably possess a chemical reaction in this

sense, and can certainly function as acids or bases, although they do not appear to be ionised.

At that time, attempts were made to define the concept of acidosis, in accordance with the ionic doctrine, in terms of the physical relationships in the blood; but these attempts were unsuccessful. We distinguish in the blood, first of all, the hydrogen concentration, which must be regarded as the measure of the physical reaction. This concentration is extraordinarily constant, remaining unchanged even when large quantities of free hydrochloric acid are administered. Not until the acidotic condition approaches its term (as in fatal poisoning with a mineral acid, or in diabetic coma) does the hydrogen ionic concentration become positively acid. It is evident, therefore, that the blood must contain substances competent to neutralise acids without any change in the ionic concentration. The most important of these buffer salts in the blood is sodium bicarbonate, and next comes the phosphate in the blood. As an index of this reserve alkalinity we can use the carbonic-acid tension in the alveoli or in the oxalate plasma, or the ionic concentration in the plasma, on the addition of measured quantities of acids.

Porges, Leimdörfer, and Markovici [163, 298] regard the carbonic-acid tension of the blood as the most reliable sign of acidosis. Van Slyke, Cullen, and Stillman [437] report that in acidosis there is no change in the ionic concentration of the blood, but that its reserve alkalinity is reduced, this finding expression in the diminished carbonic-acid tension in the alveoli. Begun, Herrmann, and Münzer [447] find, on the other hand, in an extended series of researches that large quantities of hydrochloric acid can be administered with the food, leading to a marked increase in the excretion of ammonia in the urine, without the occurrence in the blood of any reduction either of the ionic concentration or of the reserve alkalinity as manifested by the carbonic-acid tension. Not until large doses of acid have been given for a very long time, and when a general alkali impoverishment has taken place throughout the body, does the carbonic-acid tension decline, and moreover this decline seems to be evoked by grave tissue alterations. These authors' researches lead them to the conclusion that the carbonic-acid tension in the alveoli is

primarily dependent upon the carbonic-acid content of the venous blood, that is to say upon the aptitude of the blood to take up carbonic acid. Consequently, this tension cannot be an index of the acidosis, and can decline in the absence of acidosis.

Conversely, an increase in the reserve alkalinity of the blood does not indicate the existence of alkalosis, for such an increase may occur physiologically, as during digestion in consequence of the secretion of hydrochloric acid by the stomach. (Cf. van Slyke, Cullen, and Stillman [438].) Nevertheless, the alkalinisation of the blood in such circumstances will not increase beyond a certain measure, for fresh acids are continually being supplied in the food, and moreover the hydrochloric acid that has been secreted in the stomach is reabsorbed. However, grave alkalosis can be induced by repeatedly washing out the stomach during the climax of gastric digestion, so that the hydrochloric acid is removed from the body and cannot be reabsorbed. McCollum and his collaborators [1010] saw severe tetany produced in this way in cases of stricture of the pylorus.

Following the example of leading authorities, we may describe acidosis as a condition characterised by a deficiency of fixed inorganic bases in the body, leading to the increased production of ammonia. According to N. Zuntz, *the increased excretion of ammonia in the urine, in conjunction with high acidity of the urine, is the only certain sign of acidosis.* (Cf. Steenbock, Nelson, and Hart,[407, 410] and also Lyman and Raymund [962].) Many observers, such as Shaw,[1100] regard acetonuria as a sign of acidosis. But it is certain that there may be severe acidosis without acetonuria, and it is conceivable that acetonuria might occur in the absence of acidosis. Hopkins [1024] is also right in pointing out that the morbid formation of oxybutyric acid, acet-acetic acid, and acetone —a condition which can best be separately described as "ketosis"—must be clearly distinguished from the changes in the physico-chemical equilibrium which lead to a diminution in the reserve alkalinity of the blood and to a decline in its capacity for neutralising acids.

Hopkins also draws a distinction between uncompensated acidosis, in which there is a real increase in H-concentration, and compensated acidosis, in which no change in H-concentra-

tion can be demonstrated. In chronic nephritis and other kidney disorders, the ordinary protective apparatus of the body (the buffer salts of the serum, the elimination of carbonic acid by the breath, and the excretory activity of the kidneys) is thrown out of gear because the production of ammonia is disturbed, and there ensues an acidosis of renal origin, which is usually uncompensated. Nitzescu [406] and Palmer and Henderson [434] make the same distinction.

In the light of extant knowledge, it would seem to be a mistake to concentrate attention upon the composition of the blood. Very serious disorders may occur in which the composition of the blood appears perfectly normal. The blood certainly possesses to a very high degree the power of self-regulation, but this does not suffice to explain all the phenomena we are considering. It is necessary to assume that a hitherto unmentioned regulatory apparatus is at the disposal of the blood. We learn this from the frequently ascertained fact that in long-continued acidosis the body excretes less phosphoric acid and sulphur than is ingested, but that when in these circumstances fixed bases are added to the food, the balance of phosphorus and sulphur inclines strongly in the opposite direction. It follows that the blood must have temporarily deposited somewhere or other the excess of acids in the food which could not be eliminated by the kidneys or the bowel. It should also be noted that in these conditions there is a simultaneous retention of nitrogen, which is likewise excreted as soon as a sufficiency of bases is administered.

Normally, it is probable that these substances, which possess a rather high molecular weight, are not retained in the blood itself, or can exist there only for brief periods, when greatly diluted. The accumulation of such residues in the blood would certainly have bad effects, and since in the conditions we are considering they cannot be excreted in the urine, they are deposited wherever they will do least mischief. Suitable depositories are offered by the comparatively inactive tissues, such as bone, cartilage, and connective tissue. A favourite site is the subcutaneous connective tissue ; and it is here, too, that sodium chloride, an excess of which is commonly ingested, is stored pending opportunity for the excretion

of the surplus. Purely theoretical considerations convince us of such possibilities, and theory has now been confirmed by the numerous investigations of recent years. But the explanation of the process is found, above all, in two physiological peculiarities of such tissues, peculiarities by which they are sharply distinguished from the more active tissues.

In the first place, I may remind the reader of a fact which, though it was discovered forty years ago, has again and again been forgotten, namely that, whereas sodium salts and often amino-salts exert a paralysing influence on nerve and muscle, potassium salts have a stimulating effect. A discovery made by Gérard [243] gives unexpected confirmation of this. He found that functionally active organs crowded with cells, such as the muscles, the heart, the testicles, the kidneys, the liver and the brain, are comparatively rich in potassium, whereas the blood, the skin, the arteries, the lymphatic glands, cartilage, and bone, are comparatively rich in sodium. These inactive or almost inactive tissues are less injured by a fairly high sodium content, and it is a logical inference that they will also be the depositories for nitrogenous acid residues of high molecular weight.

This tendency to deposit noxious substances in regions of minor physiological importance is reinforced by the physiological proclivity of the connective tissue towards the storage of salts, and especially acid radicals of high molecular weight. The " predilection " for acid radicals is so marked that when, for example, large quantities of sodium chloride are being given in the food, and the administration of this salt is then temporarily suspended, the sodium ion is excreted first, and the chlorine ion subsequently. (Cf. Zoethout [888].) The entry of the residues into the tissues is effected by osmosis from the blood. When better conditions prevail in the blood the residues are reabsorbed into that fluid, to be oxidised there as far as possible, and ultimately excreted in the urine. (Cf. Frey [829]; Feuillé [818]; etc.) In certain disorders of the kidney, the heart, or the bloodvessels, there may be a direct increase in the concentration of the solid constituents of the tissues, sometimes amounting to double the normal, and in the case of the skin even to treble the normal. (Cf. Leva [404].) As a rule, however, the retention of these substances is attended

by increased storage of fluid in the tissues. The deposited materials carry with them so much water (infiltration of the tissues) that the percentage content of chlorine (for instance) is perfectly normal, and the retention does not become apparent until the contents of the tissue are reckoned in the dry state. (Cf. Scholz and Hinkel [377] and Rothstein [830].)

5. Paradoxical Effect of Calcium Salts in the Organism.

These peculiar relationships furnish the key to many enigmas in the metabolism of the inorganic constituents of food, but a more detailed discussion of the topic would take us too far from our proper subject. Moreover, it will be necessary to return to the matter in a subsequent chapter, so the foregoing brief indications must suffice for the present In the same connexion, however, it is necessary to refer briefly to a special instance of inorganic metabolism, one whose apparently paradoxical developments must become familiar to anyone who wishes to understand and accurately to appraise many of the experiments made in the course of modern dietetic research.

In the chemical laboratory it is possible by the addition of neutral salts to effect extensive modifications in ionic concentration, these modifications usually taking the form of a diminution of hydrogen ionic concentration. In the living organism we are unable to do this, for, as already said, the body has at its disposal a regulatory apparatus which is so manifold in its possibilities and which acts with such promptitude that the effect of doses of mineral salts is completely obscured. There is, however, one exception, which seems all the more amazing inasmuch as in this instance the administration of a neutral salt ultimately leads to an increase instead of to a reduction in the hydrogen ionic concentration. The final upshot of the consumption of this salt by an animal is the occurrence of marked acidosis. To the chemist it is at once obvious that the cause of this remarkable result cannot but be some kind of reaction which in the living organism pursues a quite anomalous course—however loath we may be, at the first glance, to entertain the notion that the chemical laws of the living organism can be different from those

of inorganic nature. In 1905, when I first drew attention to the paradox and explained it with the use of chemical formulas, my exposition aroused universal scepticism, for its improbability seems overwhelming. In essence, however, the explanation involves nothing extraordinary, nor does it entail any contradiction of familiar experience or demand the acceptance of a new system of kinetics in organic chemistry. It merely requires us to make due allowance for the fact that the animal organism is, after all, something very different from a test-tube; and that the chemical reactions that take place within it result from the collaboration of millions of cells which, despite their interdependence, are to a large extent autonomous, so that each is competent to act after its own fashion. If we study the chemical reaction in the individual cell, we find the familiar laws in operation; and it is only the collaboration of numerous cell complexes which produces an aggregate result that amazes us by its apparently paradoxical character. In other words, the ultimate result is not the outcome of a single reaction but of a series of reactions, and these reactions (here is the core of the matter) take place in various organs.

I am far from having been the discoverer of these remarkable reactions. I merely gave the explanation of facts which had long been known, though their peculiarity had not been noticed by previous investigators. Earlier in the present chapter one of these well-known facts was touched upon. I mentioned that Forbes, Halverson, and Schulz [1188] found that acidosis was increased by administering bicalcium phosphate and diminished by administering calcium carbonate. There is nothing remarkable in this, seeing that bicalcium phosphate, $CaHPO_4$, is a third-part acid salt. The remarkable point only comes to light when we know that we are dealing here with a special instance of a general rule, and when we learn that with the exception of calcium carbonate and tricalcium phosphate all the inorganic calcium salts induce acidity in the organism. Röse [192, 193, 194, 415, 623] has repeatedly noted the production of acidity in adult human beings by calcium chloride and by calcium sulphate; and Fuhge,[868] Erich Müller's assistant, noted the same thing when testing my statements by giving lime salts to children.

The strange and anomalous behaviour of calcium is explained by an observation made a great many years ago. Ernst Lehmann [4, 16] drew attention to the fact that the administration of calcium salts leads to no more than a trifling increase in the calcium content of the urine. Still earlier, Riesell [1] had shown that when calcium salts are given by mouth, the quantity of phosphates in the urine diminishes; and this observation was confirmed by Schetelig [2] and all subsequent investigators. Noorden [15] and his pupils Strauss [20, 21] and Herxheimer [22] found, however, that the administration of calcium carbonate reduces the acidity of the urine, and that the reduction in the urinary phosphates depends upon the excretion of tricalcium phosphate by the bowel; whereby these observers were led to the erroneous assumption that the calcium combined with the phosphoric-acid radical in the course of intestinal digestion. Nevertheless they recognised that a portion, at least, of the calcium phosphate must be excreted by the mucosa of the large intestines. Herxheimer also recognised that the aggregate excretion of phosphates is hardly altered by the administration of calcium. What happens, then, is that, *when calcium salts are given, a part of the phosphoric acid which would otherwise be excreted by the kidneys is diverted to the colon!* My own researches likewise showed that the greater part of the calcium is excreted by the intestine in the form of tricalcium phosphate.[97, 256]

In the urine, however, the phosphoric-acid radical is excreted as bisodium phosphate, or (as many think) in part as monosodium phosphate. The relationships, therefore, can be expressed by the following equations:

1. $3CaCl_2 + 2NaH_2PO_4 = Ca_3(PO_4)_2 + 2NaCl + 4HCl$ and
2. $3CaCl_2 + 2Na_2HPO_4 = Ca_3(PO_4)_2 + 4NaCl + 2HCl$.

Of the results of these reactions, the tricalcium phosphate appears in the fæces, and the sodium chloride in the urine. Since free hydrochloric acid cannot exist in the blood or the tissues, it immediately undergoes a reaction with bisodium phosphate:

3. $2HCl + 2Na_2HPO_4 = 2NaCl + 2NaH_2PO_4$.

The net result is that dosage with the neutral salt increases the acidity of the urine.

But before the excretion occurs, the hyperacidity has taken effect within the organism, for Fuhge (op. cit.), and I myself at an earlier date, found that the administration of calcium chloride led to an increased production of ammonia.

This is only one aspect of the paradox. The other aspect seems almost crazier. Large doses of calcium chloride induce severe losses of calcium, which may culminate in osteoporosis and osteomalacia in the experimental animals. Thus Etienne working alone,[230] and working in conjunction with Fritsch,[96] found that chloride of lime does indeed induce at the outset an accumulation of calcium within the body; but that if it is given for a long time, it induces severe losses of calcium, and that bone deformity may ensue; these evil results begin immediately if adrenalin or potassium iodide is given together with the calcium chloride. Similar results have recently been secured in Germany. The explanation has already been given. The calcium chloride induces hyperacidity within the organism, and this leads in the long run to so serious an alkali impoverishment that the last alkaline reserves of the body, those in the osseous system, are attacked and pass into solution, in order that the acids may be neutralised by the carbonates derived from the bones.

The fundamental cause, then, is the diversion of the phosphoric-acid radical from the kidneys to the intestine, and the consequent transformation of the bisodium phosphate into monosodium phosphate. It follows that all the calcium salts containing acid radicals that are incombustible within the organism must act in the same way—for instance, the calcium salts of the aromatic acids. To some degree, however, sulphuric acid is an exception, for the organism can get rid of sulphur, not only in the form of sulphuric acid, but also (in part, at least) as ester sulphuric acids which require only half the amount of alkali to neutralise them, or as non-acid compounds. Röse's experiments do in fact show that the urinary acidity is not so greatly increased by dosage with calcium sulphate as by dosage with calcium chloride. A special exception is calcium carbonate, whose acid radical can be freely discharged in the gaseous form through the lungs, so that no bases are requisite to assist in its excretion. The same considerations apply to the calcium salts of the

combustible organic acids, seeing that the terminal product of their combustion is likewise carbonic acid. In both cases, therefore, the entire calcium content of the salt remains at the disposal of the organism as a base.

It is true that the hydrochloric acid of the stomach converts calcium carbonate into calcium chloride. But this does not introduce any new hydrochloric acid into the body. Whenever hydrochloric acid is formed in the stomach, a corresponding amount of alkali is set free, and this is competent to neutralise the hydrochloric acid that is liberated when the calcium is excreted as tricalcium phosphate, so that the whole basic content of the calcium carbonate is, after all, available for the organism.

The inorganic magnesium salts exhibit the same peculiarity although not to so marked a degree as the calcium salts. The difference may depend upon the fact that the magnesium salts are in general more readily soluble, so that their excretion is comparatively easy. Furthermore the " triple phosphate " $Mg(NH_4)PO_4$, the insoluble magnesium salt, does not appear in large quantities in the faeces except in abnormal conditions.

6. The Administration of Alkalies as a Preventive of Acidosis.

Calcium carbonate, therefore, acts in the animal body as a free base in this respect, that it is competent to neutralise acids, and thus to reduce acidosis. Obviously, all inorganic bases in the free state can act in the same way, provided that they can be absorbed by the organism in a soluble form. The free bases, however, have, like the free acids, and even more than these, the disagreeable quality of being corrosive. They dissolve organic matter, and can therefore not be tolerated by the organism except in extreme dilution. The alkaline carbonates, though their corrosive influence is less powerful, are nevertheless not free from this influence, whereas calcium carbonate is, as such, insoluble and innocuous. Large doses of this salt can, in fact, be given throughout a long period without any injurious consequences, differing in this respect from the other carbonates.

It need hardly be said that the soluble bases can also be administered in the form of their combinations with the

organic acids ; these salts have little or no corrosive influence, and can be used to increase the quantity of bases in the organism. The lactates and the citrates are chiefly employed for this purpose, having a less disagreeable taste than the acetates and the formates. Thanks to the vigorous propaganda of Oskar Loew, in human medicine calcium lactate has had considerable vogue. This salt is especially useful when the patient needing calcium is suffering from gastric disorder attended by a deficiency of hydrochloric acid in the gastric secretion, for calcium lactate does not reduce the acidity of the gastric juice. In experiments on animals, bases are usually administered as lactates or citrates, whether the aim be to counteract the effects of a diet unduly rich in acids, or to provide supplementary bases in food otherwise inadequate in this respect.

For brief periods, the occurrence of acidosis in consequence of a diet rich in acids can be prevented by the administration of one base and one only ; but it must be carefully noted that any such one-sided dosage will prove unwholesome in the long run. The body needs a number of bases, and not one merely ; if satisfactory results are to be secured, the food must contain all the ingredients necessary for proper nutrition and the maintenance of life. The most bountiful administration of one single base will not suffice, for in inorganic metabolism the individual substances are mutually dependent. Clinical experience teaches that sodium bicarbonate in quantities amounting to hundreds of grammes will not prevent the death of a diabetic from coma, that is to say from acid poisoning. On the other hand, in such cases, when the use of sodium bicarbonate was no longer helpful, I have found that incipient diabetic coma can be arrested by the administration of a mixture of all the necessary inorganic bases.

7. Forms of Combination of inorganic Substances ; their Mode of Action.

This partly explains Osborne's experience that protein-free milk is by far the best provider of bases. It must of course be remembered that in protein-free milk the inorganic constituents are supplied in a form in which they can act most effectively.

In artificial mixtures of nutritive salts, these salts are all present in a readily ionisable form. As such, however, they play the part of foreign bodies in the organism, for they speedily increase the osmotic pressure to an intolerable degree. Hence they are eliminated as rapidly as possible. Many inorganic salts begin to make their appearance in the urine within ten minutes of their administration by mouth, and, speaking generally, the whole dose will have been excreted within twenty-four hours. The excretion, however, is not effected strictly proportionally to the concentration of the substance in the blood, but occurs irregularly, so that the excretion of the last traces may often be deferred for a long time. I have found that in the case of calcium and phosphorus compounds the excretion may not be completed until after the lapse of five or six days. But as far as a strong concentration in the organism is concerned, this lasts only for a brief space of time, and the period of efficacy of such substances in the body is therefore strictly limited. The reaction of the urine gives the best proof of this. When an acid-rich diet is being taken, and we aim at neutralising the excess of acid by administering inorganic bases in the form of salts, the use of litmus paper will show that the urine speedily acquires an alkaline reaction. During the night, however, the period when the great cleaning up of the organism after the day's exertions takes place, the amount of available bases is greatly reduced owing to the rapid excretion of the ionised salts, the result being that the morning urine (which contains the products of tissue change during the night) has again become acid, and is rich in uric acid although its power of holding uric acid in solution is small. In other words, when the requisite bases are supplied in the form of inorganic salts, they are excreted so rapidly that the organism suffers from alkaline impoverishment at the time when its need for alkalies is the greatest.

Conditions are very different in the case of natural nutrients. Here the inorganic bases are, to some extent at least, present in masked forms, in stable organic combination, and their presence can in many instances not be detected until after the destruction of the organic combination. To some extent, compounds of this character are even able to resist the dis-

integrating effects of digestion, as I have myself proved in the case of milk.[69, 70] In this form, the bases do not irritate the animal organism in any way, and they can be retained by the body for a considerable period, until the bases are restored to an ionisable condition by the break-up of the organic combinations. If, therefore, the organism be provided with an abundance of bases by supplying it with a food naturally rich in bases, ere long the morning urine will be found to have an alkaline reaction. In such cases the uric-acid content of the urine will tend towards a minimum characteristic of the particular diet; and at the same time the capacity for excreting uric acid, that is to say the competence of the urine to dissolve uric acid, will rise to a maximum. Thus whereas the effect of the bases in artificial mixtures of inorganic salts is restricted to a period of an hour or two after their ingestion, the bases in the natural nutritive salts remain effective over long periods, and are always on hand when the organism needs them. In my own experiments, I have found that the water in which potatoes, greens, etc., have been boiled, or protein-free milk, is speedy and effective.

These considerations perhaps explain how it is that the ill effects of acidosis, and above all emaciation on the one hand or oedema on the other, can be remedied, temporarily at least, by the abundant supply of protein in the form of meat. From the great excess of protein, large quantities of ammonia are formed, and by this the simultaneously introduced acid-formers can be neutralised and rendered fit for excretion. The inorganic bases in the meat, which to some extent are present in more or less complex combinations, are thereby reinforced, and a respite is secured, for these inorganic bases are not excreted very swiftly, and remain available to some extent for use where they may be urgently needed. (Cf. Emmet [346].)

8. Mutual Interdependence of the inorganic Substances.

If in experiments concerning complettins the investigator wishes to use mixtures of simple salts, he must always bear in mind that in long-continued experiments the effect of these mixtures does not depend solely upon the excess of

bases supplied. The law of the minimum is here in full operation; the final upshot will be determined by the substance that is present in the relatively smallest proportions. It is hardly possible to be too emphatic about this matter. *We have to think, not merely of a minimal requirement of inorganic substances in general, but also of a minimal requirement of each inorganic substance in particular.* (Cf Osborne and Mendel,[225, 719, 837] McCollum and Simmonds,[664, 1026] Barr,[1055] Hess,[1055] Külz,[840] Grabley[971].)

In this connexion it is necessary to refer to a consideration which all investigators have hitherto overlooked. It does not follow that because a mixture of salts has proved a useful supplement to a particular nutrient or to a particular form of diet, that it is an infallible dietetic supplement which will do equally good service in the case of any and every diet. If, for instance, a second nutrient contains a larger excess of acids than one which has previously been given, the natural way of dealing with this supplementary excess will be by giving larger doses of the mixture of salts. But if the undue acidity be a one-sided affair, dependent let us suppose upon an excess of phosphoric acid in the nutrient, an *optimal* effect cannot be secured by a mere increase in the amount of a general mixture of salts. The phosphoric acid will need for its excretion by the intestine a preponderant percentage of the calcium in the mixture of salts, and this will unduly reduce the quantity of calcium available for the other needs of the organism. Furthermore, the ratio between the available calcium and the magnesium or the alkalies will thereby be reduced to the disadvantage of the calcium. In such a case, therefore, we must not merely increase the dosage of the aggregate mixture of salts, but must take these peculiar conditions into account by specially increasing the dosage of calcium.

In other cases, the quantity of sulphur may be unfavourably affected in one way or another; there may be too little sodium, iron, or manganese; or there may be too much chlorine; and so on. In a word, generalisation is especially unsafe when we are dealing with this matter of inorganic metabolism. *A decision as to the composition of the supplementary mixture of salts must always be based upon an accurate analysis of the constituents of the diet.* To this matter we shall return.

9. The Utilisation of Calcium in various Forms of Administration.

A special problem is intimately connected with the foregoing—the extent to which the inorganic constituents of the various nutrients can be utilised. As far as the bases are concerned, a detailed study of the question has been made only in the case of calcium. McClugage and Mendel [748] report that in dogs the calcium in milk is better utilised than the calcium in carrots or spinach. Rose [1019, 1083] comes to the same conclusion as regards human beings, finding that the utilisation of calcium in carrots is much less efficient than the utilisation of calcium in milk. A critical study of these papers leaves a different impression on my own mind. As far as the dog is concerned, we must remember that this animal, being a carnivore, is better adapted to digest animal foods rich in protein than vegetable foods ; the dog's intestine is too short for a vegetable diet. In such experiments, dogs should be habituated to a vegetable diet before the specific enquiry begins. Next it must be noted that if the dog be not habituated to a diet of spinach or carrots, diarrhoea will ensue, involving great losses of calcium ; this is especially obvious when we recall that to supply the amount of lime contained in a very small quantity of milk, large amounts of spinach or carrots will be requisite. The mistake has been made that is unfortunately so often made by those who are studying the physiology of nutrition, of regarding " digestion " as synonymous with " utilisation." In the process of nutrition we must distinguish three stages which are to a considerable extent independent one of another, namely digestion, absorption, and assimilation. Only when assimilation is unsatisfactory, are we entitled to speak of a substance as imperfectly utilisable. If McClugage and Mendel had told us that spinach and carrots were not satisfactory as sources of calcium for dogs, they would have been within the mark, but their researches give us no information as to the degree to which the calcium is utilisable. A nutrient may be badly borne by an animal whose digestive system is ill-adapted to deal with it, but we are not entitled to infer that such portions of the nutrient as are digested are badly assimilated.

Rose, keeping four healthy human beings under observation, ascertained the calcium balance when a diet was being taken competent to supply approximately the minimal requirement of calcium. In two of the cases the experiment lasted a fortnight; in the other two, three weeks. In two instances there was a preliminary period in which the calcium needed was provided chiefly from milk, whereas in the main experiment the calcium was supplied in a daily ration of 400 grammes of boiled carrots. The experiment is so typical of the short-sighted way in which inferences are drawn from experiments on nutrition that I cannot refrain from a brief examination of the results.

Person.	Diet.	Calcium supplied in Grammes.	Percentage of Calcium from Carrots.	Percentage Increment or Deficit.
E. D. B.	Milk	0·383	0	+16
E. D. B.	Carrots	0·315	55	+17
R. S. E.	Milk	0·383	0	+23
R. S. E.	Carrots	0·315	55	− 7
E. H.	Carrots	0·261	84	+ 4
E. W.	Carrots	0·297	82	+27

From this it appears that in E. D. B. the calcium from carrots was quite as efficiently utilised as the calcium from milk, whereas in R. S. E. a deficit occurred during the carrot diet. But the retention of calcium during the milk diet was 50 % greater in R. S. E. than in E. D. B. This immediately suggests that what occurred in R. S. E. during the milk period was not an assimilation of calcium but a simple retention of calcium. Every investigator who has been engaged in researches on calcium metabolism must be aware that this substance is not rapidly excreted, and that a quantity of calcium introduced with the food is not fully discharged from the body until at least five or six days have elapsed. In such investigations, therefore, a standard diet must be selected, and must be given for a preliminary period during which the utilisation of the substance under consideration has been ascertained. Then follows the main period of the experiment, during which the test substance is added to the standard diet. In a final period, when the administration of the test substance has been discontinued, the process of

its elimination is kept under observation. Thus only can some safeguard be secured against surprises due to retarded excretion. This simple measure of precaution was not taken in Rose's experiments, and it is therefore probable that the well-marked positive balance during the milk period was partly due to such a retardation of excretion, and that the quantities of calcium that had previously been retained were excreted after the milk had been discontinued, that is to say during the carrot period, so that the balance was then falsified to the apparent detriment of the carrot calcium. We infer, therefore, that the experiments on E. D. B. and R. S. E., in which a comparison between a milk diet and a carrot diet was made, afford no justification for declaring that there is a difference in the utilisation of the calcium from milk and carrots respectively. In the cases of E. H. and E. W., there was no initial period of milk diet, and therefore no direct comparison between milk and carrots is possible. Apart from this, the experiments show such remarkable irregularities that we are entitled to challenge the accuracy of the results.

In E. H. the increment is only 4 %, whereas in E. W. it is 27 %, although the difference in the amount of lime given in the two cases was only 14 %. A strict criticism of the experiments therefore leads us to infer that in two cases the utilisation of the calcium of vegetable origin was as great as or 70 % greater than the utilisation of the calcium in milk—which is the very opposite of what Rose contends. Conversely, in the other two instances, the utilisation was less effective in the case of the calcium of vegetable origin. We may infer with some probability that the calcium in these two nutrients has the same biological value.

As a result of the observations of other medical practitioners we are entitled to draw the general conclusion that the inorganic bases are always fully utilisable so long as they are administered in such a form that they can be assimilated by the organism.

10. The Effect of Oxidation upon the biological Value of the Acid-formers.

Even when a precise analysis has informed us concerning the nature and quantities of the inorganic constituents of the food, so that we are enlightened as to what supplementary

inorganic nutrients may be required, our difficulties are by no means at an end. All that the analysis tells us is the aggregate amount of phosphorus, sulphur, etc. It may, however, very well happen that in one case this or that inorganic substance is present mainly in an oxidised (that is to say in an inorganic form), and that in another case it is present in the form of some complex organic compound. In the latter event, it may sometimes be one of the components of a readily oxidisable substance, and sometimes one of the components of a substance difficult to oxidise. The bearing on the amount of the inorganic nutrient that is requisite will vary in each case. If, therefore, we wish to ascertain an animal's requirement in respect of any inorganic substance, preliminary researches must be made to ascertain whether (when the diet is otherwise adequate) the selected method of administering the inorganic nutrient be a suitable one. Not until we know this, can we proceed with the main subject of research. The problems are further complicated because the requirement of inorganic nutrients varies in different species of animals, and also because the requirement is extensively modified by the state of the animal as regards growth and other physiological conditions, such as procreation, menstruation, gestation, lactation, etc. Above all in the case of phosphorus and sulphur we have to reckon with, not merely the absolute quantity in the food, but also the nature of the compound in which these elements are supplied. We know very little concerning the modes of combination of sulphur, and contributions to our knowledge in this respect would be most welcome. Apart from the purely inorganic compounds of sulphur, we know this element in the organism only in the form of cystein or its " anhydride " cystin, although there can be no doubt that quite a number of sulphur compounds are represented in the " neutral sulphur " of the urine. From a private communication I learn that Hopkins has recently succeeded in isolating a number of new sulphur-containing organic substances. If this is confirmed, the importance of unoxidised and organically combined sulphur will be yet further enhanced, but nothing has as yet been published on the subject.

I have already mentioned that the peculiar importance of the two sulphides to the animal organism is made manifest

by the consideration that cystin is a vitally essential substance which cannot be synthetised within the animal body. In one of their papers, Osborne and Mendel maintain [719] that the inorganic constituents of the food need only be supplied in inorganic form. But this conflicts with other reports by the same investigators, who (as we learned in the second chapter of the present work) have repeatedly noted that growth, and even the mere maintenance of weight, are impossible unless cystin be supplied ready made. Hirschstein [259] states as the result of experimental work that a number of nutritive and metabolic disorders can at least be benefited by the supply of cystin when this substance has been deficient in the food. Florence,[1156] too, emphasises the same fact, but supports his contention only by reasoning, and not by experimental data.

Though there is unanimity as concerns the need for the presence in the food of sulphur in organic combination, this is far from being the case as regards phosphorus. There is nothing to surprise us in the notion that the organism's needs for inorganic phosphorus in the oxidised form can be supplied out of phosphorus in organic combination (cf. Lipschütz,[119] Heubner,[460] and Grosser [288]), seeing that during the disintegration of organic substances within the organism the phosphorus undergoes combustion to form phosphoric acid.

Moreover, every breeder of animals know that the growing organism can utilise simple inorganic phosphorus for the building up of its osseous system ; and by Tereg and Arnold [6] the fact has been experimentally proved in the case of growing dogs. Recently, Schloss and Herbst, in an extensive series of researches, have shown that the statement is equally true of children.

We face a different problem when we ask whether the animal organism is also competent to build up organic phosphorus compounds out of inorganic. Here most physiologists make the mistake of failing to distinguish between salt-like or ester-like compounds (the so-called mixed-organic compounds) and compounds into which the phosphorus has entered as a constituent part of an organic complex. Yet the chemical distinction is vital. In the first case we have merely to do with the formation of an oxygen (ester) or amino-compound (salt)—substances in which the oxides of the phosphorus

still retain a thoroughly inorganic character. This is manifest inasmuch as simple hydrolysis or double decomposition suffices to liberate the inorganic component, so that its presence can immediately be detected by analysis. We have, indeed, a superfluity of proofs that such a combination can readily be effected within the animal organism through the simple splitting off of water or ammonia.

From these organic phosphates which are easily formed and easily destroyed in the organism, from these salt-like compounds, we must distinguish as a matter of principle the substances in which the phosphorus exists in an unoxidised or imperfectly oxidised form as a constituent of a purely organic complex, this being the form in which (in part, at least) the element is met with in the nucleoproteins. For the building up of such compounds, the phosphates as found in inorganic nature must first be reduced, that is to say hydrogenised; and in such compounds the phosphorus subsequently enters into so intimate a form of combination, that the presence of the element can only be detected after a preliminary destruction of the organic complex by oxidation. So far as the more highly organised animals, at any rate, are concerned, we do not know a single instance of such a genuine reduction of phosphorus, and the incompetence of the animal organism to achieve this reaction is the probable explanation of the inability of the higher animals to synthetise carbon chains.

Consequently, when Fingerling [199] found that, on a diet very poor in organically combined phosphorus, hens continued to lay regularly and to produce eggs containing a normal quantity of lecithin, he had merely discovered a fresh demonstration of the familiar fact that the animal body can build up phosphorus into compounds of the ester series; but the experiment throws no light on the possibility of a synthesis of genuinely organic phosphorus compounds.

Innumerable investigators have studied the problem, and almost all of them have come to the conclusion that no such synthesis can be effected within the animal body. Against some of the earlier experiments, those of Steinitz,[27] Zadik,[29] Leipziger,[30] Ehrlich,[32] and others, it is possible to lodge the objection that these experimentalists did not succeed in providing a diet free from organic phosphorus, or to complain

that the duration of the experiments was too short. The negative issue of their researches has, therefore, no demonstrative force. In other instances, as in the experiments of Gregersen,[143] the duration was ridiculously brief, no attempt was made to avoid errors due to delayed excretion, and no examination of the excreta was continued after the close of the main period of the experiment. The same criticisms apply to the experiment made by Holsti [116] upon his own person. The positive results secured by Gregersen and Holsti may, therefore, be interpreted as simply due to errors of experiment.

Only four decisive series of observations bearing on this matter have been recorded. Paton [31] has shown that when salmon are on the way to the spawning-ground, and when during this period the testicles or ovaries undergo an enormous enlargement, the phosphorus content of the ripe reproductive organs increases just as much as the phosphorus content of the muscles diminishes. Now the muscles contain a mixed-organic phosphorus compound, whereas in the ovaries and the sperm there are nucleoproteins, which must have been built up out of inorganic phosphorus. But the demonstrative force of Paton's observation rests upon the old assumption that salmon take no food while on their way up river. Pütter [87] has, however, shown that this assumption is unfounded; during their migration up river it is true that salmon are less inclined than usual to feed on other fish, but they consume plankton, and this fact cuts the ground from under Paton's reasoning.

McCollum [95] experimented on growing rats with a diet very poor in phosphorus. The rats grew in a fairly normal fashion, but they lost weight, so that McCollum's inference that the rats did not need any organic phosphorus for the purposes of their growth seems a trifle hasty.

Hart, McCollum, and Fuller [86] experimented on pigs with a diet containing very little organic phosphorus. The animals grew, but they suffered in the same way as the rats in McCollum's experiments. When the pigs were killed, the osseous system was found to be only about one-fifth as well developed as it would have been on a normal diet. Since, moreover, the experiments were not continued until the animals were old enough to reproduce their kind, they lack cogency.

All that remain, then, are the experiments of Osborne, Mendel, Ferry, and Wakeman [719] on rats. But in this case the diet was not free from organically combined phosphorus, and since the work of other investigators [119, 199, 460] has shown beyond dispute that the need for organic phosphorus is very small in comparison with the need for inorganic phosphorus, these experiments, too, lack demonstrative force. We must remember that even edestin, the protein which is most easily prepared in a pure form, is never free from phosphorus—although some of the American investigators contend that it is. I have been led by the publication of the American researches to examine a number of the edestins of commerce, and have found them all to contain phosphorus, sometimes in considerable amounts. The firm of Merck manufactured to a special order a sample of edestin of the utmost purity. This contained 0·0681 % of phosphorus (estimated as P_2O_5). On further enquiry, the manufacturers said they could not supply anything purer. My own attempts to produce an edestin free from phosphorus were equally fruitless. If a pure crystallisable protein contains so large a percentage of phosphorus, we are certainly entitled to assume that the commoner sorts of protein ordinarily employed in experiments on nutrition must contain even larger amounts of organic phosphorus. Although is so many instances we are assured that the experimental diet was free or almost free from organic phosphorus, there is adequate ground for believing that the assertions were based upon a defective analytical technique. Or, indeed, the experimentalist may have accepted the manufacturer's guarantees at their face value.

Elaborate experiments made on dogs by Rogozinski [120] and Durlach [287] gave negative results. Here, however, deficiency of complettins and bases may have been a contributory cause.

All our extant experience would seem to point to the conclusion that the amount of organic phosphorus required by the organism is very small, but that the higher animals are incompetent to synthetise such genuinely organic phosphorus compounds as they actually want. In experiments concerning complettins it is therefore essential to see that the bodily need for phosphorus in organic combination is duly satisfied.

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CHAPTER FOUR

BERIBERI AND OTHER FORMS OF POLYNEURITIS

1. Etiology.

Beriberi used to be regarded as one of the infective diseases, and as late as 1911 leading Japanese authorities made merry over the learned Europeans who took another view, who overlooked obvious facts, and fancied that in distant Europe they could discover something precise about beriberi which was hidden from Japanese scientists on the spot.[133, 136] No doubt there was a good deal to be said for the infective etiology. For instance, especial stress was laid upon the fact that beriberi, or kakke as the Japanese name it, was formerly quite unknown in the interior of Japan, and that as the railway system of the country developed the disease rapidly spread into the interior along the new routes of communication. Then, as earlier, the staple diet of the Japanese peasants was rice. If the Europeans were right in thinking rice to be a causative factor, its action, said the Japanese, could at most be indirect. Perhaps the rice was a culture medium for the infective agent. The infective theory seemed all the more probable when it appeared during the latter half of the Russo-Japanese war that the substitution of barley meal for rice did not prevent the spread of beriberi. Even to-day, quite a number of persons still cling to the infective theory, and during the late war evidence was brought forward which seemed to support such an etiology. For example, Sprawson [1231] was of opinion that the beriberi from which the British troops suffered in Mesopotamia must have had a twofold causation. Among the Indian sailors at the mouth of the Shat-el-Arab, the disease was a true avitaminosis, for these sailors were strict Mohammedans who would not

touch European food, and lived entirely on polished rice. The Goanese, who were working in the same place, but who ate European food, remained healthy. Among the Chinese coolies employed in Mesopotamia, beriberi had broken out during their transport to the country, so that this was likewise a true avitaminosis. There was, however, no improvement in the health of the Chinese coolies when they were put upon European diet; and there now ensued among the European troops, who ate abundant meat in the customary fashion, repeated epidemics of beriberi, some of them very severe. Sprawson was of opinion that the epidemiology of the disease could only be explained on the theory that among those who lived on European food it was spread by infection, seeing that the generous meat rations must have contained sufficient vitamin. The theory received official endorsement, for in the discussion on the avitaminoses,[1066] even the noted British scientist Hopkins described infection as not altogether improbable in such cases. For similar reasons, Marchoux [1155] came to the same conclusion regarding the causation of the epidemic among the Annamese soldiers in Angoulême.

In both these instances, however, the fundamental assumption that the diet had contained sufficient vitamin was contested by other authorities. Willcox,[1025, 1066] Hume and Chick,[1066] and also Wallis,[1066] pointed out that the beriberi epidemics in Mesopotamia only occurred when difficulties in the supply of fresh meat had made it necessary to feed the troops on corned beef, and that the bread in the soldiers' rations was made from the finest white flour and was therefore very poor in vitamin. In the corned beef, the vitamin had been destroyed during the process of sterilisation. (The last statement may be correct, but it is interesting to note how among the Entente States as well as among the Central European States the profit-hunting of the owners of the canning factories entailed the death of countless human beings. Udo Klünder [1384] has shown that, during the war, in the preparation of corned beef in America, the water of the first boiling, which is known to contain an abundance of vitamins, was separated from the meat and made into meat extract. In the weakly acid medium of the fresh meat it is quite probable that, but for this, a sufficiency of vitamins would have resisted

the process of sterilisation.) Regarding the epidemic among the Chinese coolies in France, Leggate [1012] reports that the staple diet consisted of polished rice, and though a meat ration was given once or twice a week, the meat was tinned.

So many instances were known in which intoxication could be excluded, that it was necessary to look for other causes. The most notable fact in the epidemiology of beriberi was that when the disease occurred in rice-eaters it was only in those who consumed fully hulled and polished rice; and that partially hulled rice, still invested with the pericarp or silver-skin, was actually able to cure the disease. A first glance at the composition of polished rice seemed, therefore, to those medical practitioners who continued to believe in Voit's dogmas concerning nutrition, to support the theory that the cause of beriberi was an insufficiency of protein and fat. The observations of Chamberlain and Vedder [156] were in harmony with this, for they found that persons fed on an inadequate supply of unhulled rice, or suffering from actual famine, developed symptoms resembling those of beriberi, and that in this disorder just as in true beriberi, the first symptom was a loss of weight amounting to at least 21 %. Eijkman [516] likewise found that polyneuritis occurred in fowls whose diet was quite inadequate, and that this polyneuritis, too, could be cured by dosage with vitamin. Segawa,[313] however, regarded the malnutrition as no more than a secondary symptom dependent upon the gradual development of a repulsion for the monotonous diet.[369] This theory conflicts with the universally known fact that the body-weight begins to decline directly the subject is put upon the pathogenic diet, long before any repulsion arises. As long ago as 1902, Hulshoff-Pol [38] drew attention to this initial loss of weight, and his data have been confirmed by all subsequent observers.

Nearly twenty years earlier, Urbeanu [8] had shown that in dietetic polyneuritis the phosphorus and potassium balance in experimental animals became negative from the very outset. Chamberlain, Bloombergh, and Kilbourne [145] pointed out that all the nutrients known to cause beriberi are poor in phosphorus and potassium. Vedder [314] confirmed this, but was of opinion that the deficiency of these substances did not suffice to

explain outbreaks of the disease. In 1904, Durham [44] had shown that the nitrogenous balance became strongly negative with the appearance of the first symptoms of the disease. These points were not fully cleared up until the comprehensive researches of Schaumann [122, 361] had shown that directly the experimental diet was begun, the balance of nitrogen, total ash, and (above all) calcium and phosphorus, became markedly negative, and grew continually more unfavourable as the disease progressed. Observations made by Aron and Hocson,[149] and by Bréaudat,[172] that the addition of meat to the diet did not cure beriberi, ran counter to the theory that the disease is due to malnutrition in the ordinary sense of the term. According to Tasawa,[336] a peculiarly typical polyneuritis ensues upon a diet in which polished rice is supplemented by white of egg or thoroughly boiled meat; and Lovelace [262] has seen a number of cases of beriberi in which the supply of protein in the food had been abundant even in accordance with the older dietetic standards. Edie, Evans, Moore, Simpson, and Webster [220] found, indeed, that the addition of casein somewhat retarded the onset of the disease; but the most plausible interpretation here is that the casein of commerce used by the experimenters was not perfectly free from vitamin.

In one respect there is something to be said in favour of the opinion of those who have held that the inadequacy of rice protein is responsible for the occurrence of beriberi, for Barr [1055] has drawn attention to the fact that experimental polyneuritis closely resembles the diseases that result from feeding with an inadequate protein—for instance, one characterised by a lack of tryptophan. This, however, can only be an accessory factor, for were it the efficient cause the addition of protein to the diet would prevent the disease, and we have learned that it fails to do so.

Bréaudat [172] found also that the addition of fat or carbohydrates was ineffective. Indeed, in monkeys suffering from beriberi, the addition of butter to the diet hastens the end.[1056] In part this remarkable result may be explained by the supposition that the provision of additional combustible material imposes upon the body an additional task with which, in its weakened state, it is unable to cope, so that the acidosis

grows worse. Moreover, my own researches [306] have shown that fats contain a far from inconsiderable excess of inorganic acids.

We have already learned that acidosis must certainly play a notable part in the development of the disease. That explains why an increase in the ingestion of carbohydrates likewise has a deleterious effect. Funk [335] emphasises this, and infers that the vitamins must play an important part in carbohydrate metabolism. Funk and von Schönborn [376] find that in pigeons fed on a vitamin-free diet, hyperglycæmia ensues, and that glycogen disappears from the liver. If, carbohydrates were withdrawn from the diet, the disappearance of glycogen from the liver was absolute; but when the fat in the food was replaced by carbohydrates there was an excess of glycogen in the liver. The addition of yeast vitamin led to a gradual decrease in the sugar of the blood and to an increase in the glycogen of the liver. We may question whether these effects may not be secondary, seeing that on a vitamin-free diet the parenchymatous organs, such as the liver, tend to atrophy. More important seems McCarrison's assumption [1056] that the increased severity of the symptoms when carbohydrates are added to the food is attributable to digestive troubles. On a vitamin-free diet, the digestion is weak in any case, so that when an abundance of carbohydrates is given, much fermentation takes place in the bowel. This leads to the production of organic acids which are directly absorbed into the blood, and give rise, since the debilitated organism is unable to effect their speedy combustion, to a well-marked condition of acidosis. Simpson [1173] and Barr [1055] come to the same conclusion. There are good general grounds for the belief that the combustion of the organic acids must be defective in such cases, inasmuch as numerous experiments have shown that the respiratory quotient is greatly reduced in animals on a vitamin-free diet, this implying that the processes of combustion are not being conducted with the habitual energy. Wellmann and Eustis [218] likewise found that the rapidity of onset of the disease is increased when the finest maize starch is given, and still more when sugar is given.

These considerations explain why overfeeding (forced feeding) with polished rice greatly accelerates the outbreak of the disease.[145]

This leads us to another theory as to the origin of beriberi. Since it is no longer possible to accept the theory of infection in the ordinary sense, and since there is overwhelming evidence that the malady is often induced by a diet of polished rice, an attempt has been made to save the honour of the microbes by maintaining that the rice must have been damaged. This theory secured support from the fact that the progressive degeneration of the nervous apparatus actually resembles in its morbid anatomy that which is encountered in diseases which are unquestionably toxic.[271] Maurer [45] suggested that the cause of beriberi must be oxalic-acid intoxication originating in the intestine. Others, such as Ekelöf,[47] F. Clair,[1077] Marchoux,[1155] Samelson,[1246] etc., incline rather to assume that there is a bacterial production of toxins in the intestine, owing to the decomposition of the rice. But Eijkman [321, etc.] and others have pointed out that beriberi sometimes occurs without any sign of intestinal disorder, and when the soundness of the polished rice is above suspicion.

Other observers, such as Bucco,[1214] for instance, consider it more probable that the rice diet must contain some poison analogous to that found in cotton seed, and that in the unpolished rice this poison is neutralised by the vitamins contained in the pericarp. In favour of such a view may be quoted the observations of Yamigawa, Koyama, Midorikawa, and Mogi,[248] who found that the injection of fermented watery extract of rice greatly accelerated the outbreak of the disease, but only in animals that were being fed on polished rice. Sawazaki [272] likewise found that in fowls the repeated injection of milk from women suffering from beriberi gave rise to polyneuritis. We must, however, point out that the considerations previously adduced entitle us with perfect confidence to interpret these observations in a very different fashion. Strong and Crowell,[223] experimenting on human beings, showed that the pathogenic cause could not possibly be a toxin, but must unquestionably be found in the absence from polished rice of some vitally important nutrient. Lovelace [262] pointed out that the disease may also occur in persons on a mixed diet.

The study of all these morbid phenomena and their etiology would certainly have been impossible had not Eijkman [19] proved as early as 1896 that feeding with polished rice can

induce in fowls a polyneuritis which closely resembles human beriberi. In this connexion it may be of interest to note that polyneuritis gallinarum has recently occurred on a large scale, as an outcome of wartime feeding, in Holland among ordinary domesticated fowls.[975] This proves that the experimental polyneuritis previously observed was not simply an artificial product of laboratory conditions, but a nutritive disorder perfectly analogous to beriberi. It has now, therefore, become possible to study in animals the complicated problems concerning this enigmatic disease more intimately and more speedily than could be done in human beings in hospital.

Holst and Frölich [62, 63, 64, 65, 100, 105, 107, 186] had already noted that not only polished rice, but most other cereals from which the bran has been very thoroughly removed and which have been finely ground and sifted, induce scurvy in pigeons and barndoor fowls. When unhulled, these cereals are harmless to such birds, but bread made from fine flour is extremely injurious. The same observers discovered that raw meat does indeed cause general disorders in fowls, but that the birds become affected with polyneuritis only when the meat had been boiled for a long time, or superheated (110° to 120° C.). In like manner, potatoes that had been long boiled induced polyneuritis in fowls. Hart, Halpin, and McCollum [612] also showed that unhulled cereals were harmless to fowls, provided that calcium carbonate was added to the food in order to prevent the incidence of other diseases than beriberi. According to Weill and Mouriquand,[627] hulled maize and sterilised maize both cause polyneuritis, whereas the hulls of raw maize have an antineuritic influence, and, according to Clementi,[529] fowls which have been affected with polyneuritis by being fed on rice can be cured by giving them wholemeal from maize. According to Schaumann,[361] too, the whole maize is harmless to pigeons.

Nevertheless, cases of beriberi have been reported in which the pathogenic agent was unquestionably unhulled rice, and not polished rice. [1077, 1155, 1181] The most reasonable explanation of these instances is to suppose that in such cases the rice had been kept too long in store.

It has long been known that green peas and fresh beans are rich in vitamins. This is especially true of the katjang-idjo

bean (Phaseolus radiatus), renowned as a remedy for beriberi. As early as 1902, Hulshoff-Pol [38] prepared an extract of katjang-idjo which was successful in curing beriberi. Moszkowski [174] expressly declares that when an exclusive diet of polished rice is producing beriberi, the occurrence of the disease can be prevented by the addition of comparatively small quantities of this bean to the daily ration. Schaumann [361] confirms the statement that katjang-idjo has both a prophylactic and a curative action in beriberi; but adds that the remedial influence of the bean declines as it gets older, and that beans which have been stored for five years are quite ineffective. This accords with the report of Weill, Mouriquand, and Michel,[496] that sterilised meat will induce polyneuritis in cats more rapidly in proportion to the time the meat has been stored. The same observers found that raw frozen meat or salt meat was well borne by cats if fresh, whereas when it has been long kept it is known to be free from vitamins and to have a pathogenic influence.

I must repeat that in the case of seeds, too, the method of preparation is of much importance. Osborne and Mendel [493] found that there was abundant vitamin in cotton seed, but Rommel and Vedder [461] report that fine cottonseed meal, as an exclusive diet or as an extensive supplement to hay, induces polyneuritis in cattle. In like manner, pigs fed on hulled rice, cottonseed meal, or a mixture of maize meal and cottonseed meal, speedily became affected with polyneuritis. In conformity with the observations of Holst and Frölich, Little [261] reports the occurrence of beriberi in St. Anthony (Newfoundland) and Labrador in persons nourished almost exclusively on fine wheaten flour. In the pig, too, according to Hart, Miller, and McCollum,[515] large quantities of fine wheaten flour give rise to polyneuritis.

The question is greatly complicated by the circumstance that the same nutrient has very different effects in different species of animals. We have seen that maize is harmless to fowls and pigeons; and according to Holst and Frölich [186] rats remain healthy on a maize diet,—an observation confirmed by Schaumann. Conversely, Schaumann's experiments show that maize induces marked polyneuritis in rabbits; Holst and Frölich, and also Schaumann, have found that it causes

scurvy in guineapigs; whilst Weiser [258] states that pigs fed on maize perish from general malnutrition. Again, according to Hart, Halpin, and McCollum,[612] fowls fed on wheat remain healthy, whereas pigs and rats develop polyneuritis on this diet; and Holst and Frölich inform us [65] that guineapigs fed on wheat suffer from scurvy.

The varying reaction of different species of animals to an identical diet is still a complete enigma, and in my opinion insufficient attention has been paid to the matter. Speaking generally it would seem that graminivorous birds thrive on whole grains, but suffer from polyneuritis when the grain is hulled. In mammals, on the other hand, grain feeding may cause polyneuritis in certain circumstances, especially in rodents (except for the omnivorous rat), which are highly susceptible to acidosis. In many mammals, however, a grain diet induces scurvy instead of polyneuritis; while some animals perish from general malnutrition owing to the inadequate supply of inorganic nutrients in the grain. When grain has been very thoroughly hulled, almost all animals, human beings included, become affected with polyneuritis. Are these variations due to varying requirements in respect of vitamin; or are the polyneuritic disorders due to the absence of various vitamins which act differently in different species of animals, or are essential to different species in a varying degree?

Holst and Frölich (op. cit.), experimenting on guineapigs, found that these animals on an exclusive cereal diet invariably succumbed in from fifteen to forty-six days. In sixty-five fatal cases, sixty-three were well-marked instances of scurvy, and only two were instances of polyneuritis. It is true that a large number of the animals dying of scurvy were found on post-mortem examination to have degenerative changes in the finer ramifications of the peripheral nerves, but there had been no paralytic symptoms. Considering this observation in the light of what has previously been said, its interpretation becomes easier when we recall that rodents are extremely sensitive to acidosis, which in these animals always leads to hæmorrhages, and frequently to the occurrence of oedema. If their food be characterised by a lack both of vitamin and of the antiscorbutic complettin, the effect of the latter deficiency will be reinforced by the acidotic influence of the food, so

that scurvy will develop unless there be some special predisposition to nervous disease, a predisposition either congenital or acquired. It is in these exceptional instances of predisposition that polyneuritis develops. But the fact that in such cases, also, the bones were found to be "as thin as paper," shows that scurvy or acidosis existed as a complication.

We have already learned that beriberi in human beings and polyneuritis in other animals are not solely associated with an exclusive rice diet, but may occur when various other nutrients are given. Even when these pathogenic nutrients are given in conjunction, and even when they are given (of course in preponderant quantities) in association with nutrients that have a curative effect on polyneuritis, polyneuritis will ensue, as happened in the case of the British troops in Mesopotamia, and as was observed by Dufougeré [1244] in French Guiana. Lovelace [262] reports a case of beriberi observed by himself in which the patient had been taking a mixed diet. Dickenson,[426] and also Smith and Hastings,[286] noted the occurrence of this disease in persons taking an extremely varied diet which seemed to comply with all the hitherto accepted essentials of an adequate nutrition. "Ship beriberi," which also arises in persons taking a mixed diet, cannot be considered here, since nervous symptoms are entirely lacking in this form of the disease. The whole clinical picture of ship beriberi assimilates it rather to malnutritional oedema, and we shall return to the matter in that connexion.

When beriberi occurs in persons taking a mixed diet, it will be found: (*a*) that some of the important nutrients have been subjected to a preserving process involving exposure to excessive or unduly prolonged heat; or (*b*) that the cereals in the diet have been subjected to too extensive a hulling process in the mill; or (*c*) that other important constituents of the food have, in preparing them for the table, been boiled and that their vitamin content has passed into the cooking water and been thrown away.

This account of the etiological importance of diet in relation to the onset of beriberi may conclude with a reference to the fact that both Cooper [269] and Vedder [235] have found that the use of alcohol does not appear to accelerate the onset of beriberi or to aggravate the course of the disease.

2. Isolation of Vitamin.

The first attempt to isolate the antineuritic principle was made by Hulshoff-Pol [38, 68, 626] in 1902. Having prepared a watery extract of katjang-idjo beans, he added lead acetate to form a precipitate; the filtrate was then freed from lead by means of sulphuretted hydrogen; by subsequent evaporation at the ordinary temperature he secured an acid crystalline substance to which he gave the name of X acid. It had prophylactic virtues against beriberi, and was a useful remedy in cases of that disease. McCollum and Simmonds [670] subsequently isolated vitamin from haricot beans. Having extracted these with 95 % alcohol, they got rid of the alcohol by evaporation, freed the residue from fat by treatment with ether, mixed it with dextrin, and precipitated the active principle in conjunction with the dextrin by means of absolute alcohol. These observers recorded as a remarkable peculiarity that vitamin, which is ordinarily insoluble in acetone and benzene, can be extracted from the dried dextrin precipitate by the use of acetone or benzene. This statement has not been confirmed by any other investigators.

It was natural that other early attempts to isolate vitamin should have been made in the case of rice grains or the silver-skin of rice (rice polishings). In 1910, Fraser and Stanton [108] reported that the active principle could be extracted from rice by means of alcohol. The next year, Funk [155] extracted the hulls of rice with alcohol, freed the solution from alcohol, dissolved the residue in dilute sulphuric acid, and then precipitated with phospho-tungstic acid; the precipitate was treated with baryta water, and after the excess of baryta had been removed by the addition of sulphuric acid, the filtrate was first purified with an excess of silver nitrate, and then the vitamin was precipitated as a double salt with silver nitrate by the use of baryta water. From this precipitate it was possible to extract a crystalline preparation, which proved to be the nitrate of an organic base.

Subsequently the method was much modified, but the essentials of the process remained unchanged—the crude vitamin was isolated by the precipitation of a sulphuric-acid solution by means of an exactly adequate quantity of phospho-

tungstic acid. Tsuzuki and Shimamura [136] improved the method. Having driven off the alcohol from the first alcoholic extract, they removed the fat from the extract by the use of ether. They were then content with decomposing the phospho-tungstic-acid precipitate by means of baryta, subsequently freeing the solution from baryta by treatment with sulphuric acid, and then evaporating to a syrup. By this process they secured a thick syrup, acid in reaction, and representing 0·3 % of the material originally extracted. They named the product aberi acid.

Schaumann [122] prepared his crude vitamin in the first instance by extracting the silver-skins of rice (rice polishings) with about ten times their weight of 96 % alcohol, driving off the alcohol by evaporation on a water-bath at a moderate temperature in a strong air-current, and removing the fat from the extract by the use of acetone. He subsequently secured a purer product by the following process. Having made an extract with water, or better still with dilute (0·2 %) HCl, he treated the extract with 96 % alcohol, precipitated the filtrate with sublimate solution, and decomposed this precipitate. At a later date, [361] he seems to have used 0·3 % HCl, but he states that extraction both with this and with alcohol is far from being successful. Hence we can understand the experience of Abderhalden and Lampé, [289] who found that extraction with alcohol did not notably impair the curative virtues of rice bran.

Since Funk's method involves serious losses of the active principle, Tsuzuki [320] attempted to secure a crude preparation more highly charged with vitamin. Having extracted with 60 % alcohol, he evaporated to a syrup, which he saturated with ammonium sulphate until the proteins it contained were precipitated; the filtrate was then freed as much as possible from ammonium sulphate by the plentiful addition of alcohol; the solution having been once more concentrated, was again precipitated, this time with absolute alcohol, and the filtrate then concentrated by evaporation at a temperature of from 60° to 80° C. to form a thick extract, brownish in colour. To this, Tsuzuki gave the name of antiberiberin. One kilogramme of rice polishings yielded fifty grammes of antiberiberin. According to Schaumann [361] it was almost entirely ineffective.

Funk [273] endeavoured to purify his own crude vitamin by fractional crystallisation, thus securing two crystalline substances. One of these was apparently nicotinic acid, and the other was a hitherto unknown nitrogenous body of high molecular weight.

Before this, Tsuzuki, Shimamura, and Odake [210] had tried to obtain pure vitamin. The crude product resulting from the decomposition of the phospho-tungstic-acid precipitate was precipitated with tannic acid and subsequently purified in the form of a crystalline picrate. The substance thus obtained, known as oryzanin, was found by Drummond and Funk [390] to be quite ineffective.

The purest preparation hitherto secured is that made by Hofmeister.[1113] He treated rice polishings and rice husks three times in succession with twice their bulk of 80 % alcohol in the cold, evaporated the extracts in vacuo, treated the residue with hydrochloric acid even as strong as 3 %, and then extracted the fatty matter with ether; the ether was then driven off in vacuo at a low temperature; a thick syrup resulted, and this was purified by precipitation with 80 % alcohol. The filtrate, having been freed from alcohol in vacuo, was rendered slightly alkaline by the addition of sodium carbonate, and then precipitated with Kraut's potassium-bismuth iodide solution, care being taken to avoid the development of a strongly acid reaction. After five hours, the precipitate was removed by siphonage, decomposed by trituration with silver carbonate, and the preparation was then promptly filtered. The filtrate was freed from silver by weak acidulation with hydrochloric acid, filtered once more, and evaporated in vacuo to near dryness. The residue consolidated to form a faintly tinted, deliquescent mass with a radiating crystalline structure, and from 5 to 10 milligrammes of this sufficed in pigeons affected with polyneuritis to remove the paralytic and convulsive symptoms for from 8 to 10 days. By the gold hydrochloride method a pure substance could be prepared from this material, and to the purified preparation Hofmeister gave the name of oridin (probably a dioxipiperidin), which however proved quite inefficacious. Hofmeister supposes that the efficacy of the crude material must depend upon the presence of small quantities of some constituent

which is lost during the process of purification (in that case it must possess amazing potency). His alternative explanation is that the virtues of the crude material are destroyed by the purification.

Most investigators, however, in their attempts at the isolation of vitamin, have recourse to yeast as a more readily accessible substance. As early as 1910, Schaumann [122] secured an effective extract as follows. Having removed the fat from the yeast with ether, he extracted the residue with 0·2 % HCl, precipitated the extract with an abundance of 96 % alcohol, repeated the solution and precipitation, and finally washed the precipitate on the filter with alcohol and ether. Edie, Evans, Moore, Simpson, and Webster,[220] having extracted the fat from yeast with ether, treated the residue with cold 96 % alcohol, and evaporated the alcoholic extract in an air current. The residue was then dissolved in 0·2 % HCl, purified by Funk's phospho-tungstic acid and silver-nitrate process, microscopic crystals amounting to 0·0038 % of the original yeast being ultimately secured. According to Schaumann,[232] if the process be arrested at the stage of decomposition of the phospho-tungstic-acid precipitate, an effective product is secured, but this contains considerable quantities of an impurity (perhaps cholin) which has a toxic action. He has therefore modified the process in this way.[361] The filtrate after precipitation of the baryta by sulphuric acid is evaporated at a low temperature to a syrupy consistency, dried with silica in a vacuum exsiccator, finely powdered, and steeped twice in succession for forty-eight hours in absolute alcohol with three drops of dilute sulphuric acid. On drying this alcoholic extract, he secured an active crystalline residue, which was manifestly a mixture. But in this case, as in that of the rice vitamin, the activity of the preparation was destroyed in the purification of the separate components of the mixture. (Cf. Seidell [1443, 1484].) Funk, moreover, had earlier had the same experience with yeast vitamin.[273] He had isolated from the crude vitamin three crystalline substances, one of which appeared to be nicotinic acid, whilst the other two were nitrogenous substances of high molecular weight.

Vedder and Williams,[284] in their experiments with rice bran, had found that the vitamin in the natural product must

certainly exist in a combined form, probably as the union of a pyrimidin base with nucleinic acid, for the full efficacy of the extract was not developed until after hydrolysis. They found, also, that Funk's method of preparation must be attended with great losses, for the original hydrolysate was from twenty to twenty-five times more effective than the vitamin that could be extracted from it.

In the case of yeast, likewise, it appears that the full efficacy is only developed after the autolysis of the yeast. As a rule, therefore, in subsequent investigations autolysed yeast has been used as raw material, and here again Williams and Seidell [560] noted that the crystalline crude vitamin lost its efficacy completely during the process of recrystallisation. Abderhalden and Schaumann [803] subsequently prepared an effective crude substance by simply precipitating the alcoholic extract of the hydrolysed yeast with acetone or mercuric chloride.

Sugiura [776] reports an entirely new way of obtaining vitamin. He puts the dry yeast in a collodion bag, and fills up with water, or better with 5 % sodium-chloride solution. The vitamin gradually makes its appearance as a crystalline powder on the outer surface of the bag, and can be secured by merely brushing it off. I am not aware that this method has been checked by any other observer.

Osborne and Wakeman [978] attempted to secure an active highly concentrated crude vitamin in an extremely simple manner. They gradually scattered dry yeast into boiling water to which ten cubic centimetres of 1 % acetic acid had been added. After two minutes' boiling, the whole was centrifuged, and the yeast was washed once more with water acidulated with acetic acid. The purified solution was gradually diluted with alcohol, and precipitates were secured with a content of 52 %, 79 %, and 90 % of alcohol by weight respectively. The bulk of the vitamin was in the second precipitate, and represented about 6 % of the total dry matter in the yeast. Recently Fränkel and Schwarz [1323] have attempted to secure vitamin in a pure state, but with the aid of a quite unsatisfactory control process. Having made an alcoholic extract of yeast, they removed the fatty matter with ether and precipitated the residue with lead acetate.

The filtrate was freed from lead with sulphuric acid, and precipitated with concentrated mercuric chloride solution, the precipitate being then treated once more with sulphuric acid. The filtrate from mercuric sulphate was freed from sulphuric and hydrochloric acids with lead oxide and silver carbonate, and then concentrated in vacuo. By degrees, there crystallised out a substance, which, however, proved inactive. The highly active mother solution was purified with picrolonic acid, the filtrate was precipitated with a sufficiency of phospho-tungstic acid, and the precipitate decomposed with baryta water. The filtrate was freed from baryta by the addition of 50 % sulphuric acid, refiltered, and concentrated in vacuo. The yield was 0·2 % of a very active syrup. Attempts to extract the free base from this by treatment with amyl-alcohol after alkalinisation with bicarbonate, were fruitless.

A somewhat new method has been adopted by Myers and Voegtlin,[1144] who omitted the precipitation with phospho-tungstic acid. Dried yeast was powdered, and boiled repeatedly in methyl alcohol containing 1 % of concentrated hydrochloric acid, the alcohol was distilled off, the residue was dissolved in the smallest possible quantity of 1 % hydrochloric acid, the solution was shaken up with ether, and the chlorine was then precipitated with hot aqueous silver acetate solution. The filtrate was treated with a considerable excess of silver acetate solution, and baryta water was added until an alkaline reaction began to appear. The resulting precipitate was decomposed with sulphuric acid and sulphuretted hydrogen, the solution being freed in the ordinary manner from these two ingredients, and then concentrated in vacuo. From the concentrate, histidin and similar substances were precipitated with mercuric sulphate, and the filtrate was then treated with absolute alcohol. The resulting precipitate was first freed from mercury by the use of sulphuretted hydrogen, then freed from sulphuric acid by the use of lead acetate, and finally freed from lead by the use of sulphuretted hydrogen. When the liquid was concentrated in vacuo in the presence of caustic soda, spindle-shaped crystals gradually formed, and these were extremely active. If, however, the crystals were removed from the mother liquor, and an attempt made

to purify them by washing with absolute alcohol, they completely lost their activity and became transformed into prisms.

We see, then, that there is no difficulty in preparing effective extracts from various foodstuffs. But the purification of these extracts is attended with a notable loss of material, and the activity of the preparation seems to disappear at the very moment when the last stage on the way to purity is reached. The meaning of this remarkable behaviour will be considered later.

3. The Properties of Funk's Vitamins.

All that we as yet know concerning the antineuritic principle assures us that it is readily soluble in acidulated water or alcohol. In pure water, or 95 % alcohol, it is soluble with great difficulty, so that these menstrua extract it quite incompletely. In absolute alcohol, ether, acetone, benzol, benzin, chloroform, and acetic ester, it is quite insoluble; and yet McCollum and Simmonds [670] make the remarkable assertion that acetone, though it cannot dissolve vitamin directly out of plants, can dissolve it out of the concentrated alcoholic extracts of these. The same authorities declare that when vitamin has been precipitated by dextrin and alcohol and the precipitate dried, the vitamin can be extracted from this precipitate by benzin. Should the statement be confirmed, we shall have a far simpler method of isolation than the laborious and wasteful procedures hitherto employed, namely precipitation by phospho-tungstic acid, silver, or mercury.

Chamberlain, Vedder, and Williams [196] were the first to notice the absorption of vitamin by animal charcoal. It is possible that this might be made the basis of the method for its isolation; but we have to note that these authorities declare that the vitamin cannot be re-extracted from the charcoal either by water, alcohol, or ether. Various writers [537, 560, 666] have noted that vitamin can be absorbed by either purified or ordinary fuller's earth. On the other hand Emmet and McKim [666] tell us that silica does not absorb it. Another observation, which may lead to a comparatively easy method of purification, is that made by Voegtlin [511]

that mastic emulsion will absorb vitamin. This is especially important in view of the fact that Voegtlin and White have noticed that adenin and kindred bases are not taken up by this absorbant. From such an absorbate, by dissolving it in benzin and shaking it up with acidulated water, a fairly pure product could be speedily obtained.

The enormous losses attendant on the various methods of purification do not seem to depend only upon the peculiar instability of vitamins. Perhaps the main reason is that vitamin is, as Cooper [269] tells us, precipitated from its solutions in conjunction with any precipitate of a nascent metallic sulphide. When we remember that attempts to purify vitamin always entail its precipitation as a double salt of silver or mercury and its subsequent freeing from the metal by treatment with sulphuretted hydrogen, or else that the solutions are purified by treating them with lead salts and subsequently precipitating the lead with sulphuretted hydrogen, it will be readily understood that extensive losses cannot fail to ensue.

Vitamins are not precipitated from acid solutions by lead acetate, calcium chloride, barium chloride, or silver salts; nor from alkaline solutions by phospho-tungstic acid. On the other hand when the vitamin solution has been rendered alkaline by baryta water, the vitamin is precipitated both by barium chloride and by silver salts; and in the foregoing section we have frequently noted that it is precipitated by phospho-tungstic acid in solutions weakly acidulated with sulphuric acid. According to Schaumann,[122] copper acetate induces abundant precipitation in the crude vitamin solution, but inasmuch as Funk [205] tells us that no precipitation is induced by copper salts in purified solutions of vitamin, the precipitation observed by Schaumann must have depended on the presence of impurities.

Regarding the reaction to mercury salts, Osborne and Wakeman [978] state that vitamin is precipitated by mercuric chloride, whereas Myers and Voegtlin [1144] actually free vitamin solutions from other bases by the use of mercuric sulphate. Probably the precipitation observed by Osborne and Wakeman was likewise due to the presence of such bases as adenin, histidin, etc., as impurities.

According to Tsuzuki, Shimamura, and Odake,[210] vitamin forms precipitates with picric acid and with tannic acid. According to Osborne and Wakeman[978] the precipitation with picric acid does not occur unless the reagent is added in suitable excess.

The vitamins are dialysable,[156, 182] and are comparatively resistent to acids. Dilute sulphuric, hydrochloric, and nitric acids, have no effect on them, and according to Schaumann vitamin is unaffected by long treatment with 10 % sulphuric acid. On the other hand, most investigators agree in stating that it is very sensitive to an alkaline reaction, especially to caustic alkalies. Still, even by these, vitamin is not instantaneously destroyed; its destruction requires a time which varies in accordance with the concentration of the alkali, But there are two observations sharply conflicting with these statements. According to Williams and Seidell,[560] the absorbate into fuller's earth is insensitive to alkali, and the vitamin can actually be extracted from the absorbate by a dilute alkaline solution. Daniels and McClurg[834] tell us that the vitamin in haricot beans, soy beans, and cabbage will even resist superheating (120° C.) in the presence of sodium bicarbonate. In this instance we are not told whether the amount of sodium bicarbonate added was sufficient to make the menstruum markedly alkaline.

Reports concerning the sensitiveness of vitamins to heat are contradictory. According to Fujitani[121] the vitamin of rice is destroyed by prolonged heating of the rice bran at 100° C. Funk[323] reports that the boiling of milk suffices to reduce its vitamin content, and the same authority[334], as also McCollum and Davis[455] agrees in stating that casein no longer contains vitamin after it has been boiled. Abderhalden and Lampé[289] report that fowls fed on rice become affected with polyneuritis sooner when the rice is boiled than when it is raw; but Funk[357] points out in this connexion that fowls consume a larger quantity of boiled rice than of raw, and we have repeatedly noted that an excess of carbohydrate food accelerates the onset of polyneuritis. When the fowls are given a definite ration of rice, it does not matter whether the grain is boiled or raw.[334] A remarkable observation is that of Holst, who found that fowls fed on boiled potatoes[62]

became affected with polyneuritis, whereas fowls fed on dried potatoes [65] developed scurvy. The vitamin would seem, therefore, to be thermostable in comparison with the complettin C.

Higher temperatures definitely injure vitamin. Weill and Mouriquand,[470, 495] Voegtlin,[536] Hogan,[646] and Hopkins and his collaborators [1066] agree in reporting that an exclusive diet of cereals, meat, or vegetable foods that have been sterilised at 120° C., invariably gives rise to polyneuritis. Weill and Mouriquand [497] noted the same thing in the case of sterilised unhulled rice; and it has also been noticed in the case of sterilised maize.[632]

Various observations seem, however, to conflict with the foregoing statements. According to Chick and Hume [596] yeast containing 65 % of water loses no more than an insignificant amount of its protective influence through being kept for one hour at a temperature of 100° C. They say that the vitamin in the wheat germ can bear without damage two hours' exposure to a temperature of 100° C., but at 120° C. it is rapidly destroyed. In the already quoted paper by Daniels and McClurg we read that the vitamin in haricot beans, soy beans, and cabbage will bear heating for half an hour at 100° C., and even at 120° C., although bicarbonate of soda has been added; but after this treatment most of the vitamin has passed into the water. According to Röhmann,[472] the baking of food for one and a half hours does not destroy the vitamins. Barsickow [304] reports that yeast that has been heated to 120° C. is still able to cure polyneuritis; and Figueira [1046] succeeded in curing beriberi with sterilised beans. According to Osborne and Mendel,[702] boiled meat still contains considerable quantities of vitamins. The conflict of evidence is explained when we recall that in the sterilisation of large masses of compact foodstuffs, after exposure for one and a half hours to 120° C., the heat in the centre does not exceed 70° C. Bidault and Couturier [1250] found that by the cooking of meat the vitamin content was markedly diminished when the temperature of the joint reached 90° C. in the centre, and that the curative effect of meat in beriberi declined notably as the duration of the exposure to heat increased.

As a supplement to the above it may be mentioned that

Funk [510] found radium to have no effect upon the activity of vitamin; and that Zilva [916] makes a similar report as regards ultraviolet light.

Not much is known regarding the colour reactions of vitamin. What seems to be a fairly pure preparation assumes a deep blue colour when treated with phsopho-molybdic-phospho-tungstic acid; but it gives no colour reaction with phospho-tungstic acid alone in acid solution [488]; whereas when rendered alkaline with soda solution, a blue tint develops.[560] We must remember that these reactions are common to a very large number of substances, so that we can confidently assert that they are not specific, and we may with considerable probability attribute them to the presence of impurities.

In the foregoing we have seen how extraordinarily difficult it is to prepare a vitamin that is even moderately pure. Hence our knowledge of the composition of the vitamins is scanty The literature of the subject, for instance one of Schaumann's papers,[122] contains elementary analyses of active preparations, but it is obvious that these latter were impure, so that the results of such analyses do not justify any inferences as to the real composition of the vitamins. Funk,[155, 205] who secured his vitamin as a nitrate, gives its composition as 55·63 % C, 5·29 % H, and 7·68 % N, deducing the formula $C_7H_{16}NO_3 \cdot HNO_2$. He regards it as a pyrimidin derivative, and considers it to be either a constituent of nucleinic acid or to be combined with nucleinic acid. There is much evidence in support of this view, especially the statement of Chamberlain and Vedder [156] that vitamin is formed from the decomposition of bean protein, and also the frequently observed fact that autolysed yeast has a more powerful action than yeast in the original state. Hofmeister [1113] gives a similar composition for his oridin hydrochloride. The formula is $C_5H_{11}NO_2 \cdot HCl$. It has a melting-point of 240° C., and may perhaps be a dioxypiperidin. Perhaps connected with this is Abderhalden and Schaumann's observation [803] that among the hydrolysis products of autolysed yeast there was "aschamin," which appeared to be a dimethylpropenylamin.

A survey of the whole series of investigations and of the attempts to obtain the antineuritic principle in a pure state

makes it perfectly clear that we have not to do with one single vitamin, but with a whole class of more or less similar compounds. In one of his subsequent publications [273] Funk reports that he has been able to isolate from rice hulls two nitrogenous products, one of which seems to have been nicotinic acid, whilst the other appeared to have a far more complex composition than had hitherto been supposed, the formula being $C_{26}H_{20}N_4O_9$. From the extract of autolysed yeast he secured, in addition to nicotinic acid, two other bases, with the respective formulas $C_{24}H_{19}N_5O_9$ and $C_{29}H_{23}N_5O_9$.

When it became clear that these active bodies whose absence was attended by the occurrence of polyneuritis were nitrogenous, it was natural to think of studying the relationship to neuritis of the other nitrogenous compounds known to exist in the animal body or to be frequent constituents of the food. Thymin, cytosin, uric acid, and guanin,[265, 317] also cholin,[284, 361] purin,[284] neurin, and betain,[361] arginin, asparagin histidin, and other amino-acids,[196] and adrenalin,[289] proved quite inactive in this respect. On the other hand a number of substances were found competent to postpone death from polyneuritis for days or hours, though not positively curative like vitamin. Thus strychnine [311] delayed the fatal issue; and chinin and cinchonin, in contradistinction to cinchonidin, had at least a transient efficacy.[269] According to Abderhalden and Lampé,[289] allantoin was inactive; but Funk [317] states that its administration was followed by definite improvement, so that life was prolonged for two or three days. Hydantoin actually prolonged life for nine days. According to the same authority uracil led to an alleviation of the paralyses, and prolonged life for from two to six days. Whereas Williams and Seidell [560] declare adenin to be quite inactive, according to Funk, this substance, and also hypoxanthin and xanthin, though they have no effect on the paralytic symptoms, can nevertheless prolong life in pigeons for from thirty hours to five days. Paraxanthin had a certain antineuritic effect on one occasion, but in three other cases was inactive. Thymonucleinic acid led to marked improvement, and prolonged life for from nine to fourteen days, whereas yeast-nucleinic-acid gave only a four-days' respite. Schaumann, who noted that yeast-nucleinic acid had a definite, though transient,

beneficial effect, [73,122] is, however, right in insisting that in view of the great variations in the duration of life in such cases, a brief retardation of the fatal issue can hardly justify any inferences. Nor has the intensity of the paralytic symptoms much significance, for these vary greatly from case to case.[361] The same criticism applies to the observation of Abderhalden and Ewald,[683] that atropin, in contradistinction to pilocarpin, seems to mitigate the attacks to some extent.

Weight must, perhaps, also be ascribed to the objection which Cooper [269] has made to his own experiments on the effect of chinin and cinchonin. He found that these substances could sometimes relieve the paralytic symptoms, but that they were quite ineffective in this respect when they had first been kept for six hours at a temperature of 125° C. He infers from this that in the manufacture of the quinine bases traces of vitamin from the cinchona bark sometimes cling to the product, and this impurity gives the bases an illusory appearance of activity as antineuritics.

Funk [974] had entirely unfavourable results with phloridzin, and also with adrenalin, thyroid extract, and parathyroid extract, which all hasten the onset of the disease, increase the loss of weight, and sometimes hasten considerably the fatal issue.

New paths of enquiry were opened when Funk published his supposition that vitamin was a derivative of pyrimidin, and still more when he was able to detect nicotinic acid among the constituents of crude vitamin. He ascribes the curative effects of rice vitamin and yeast vitamin to the compound formed by nicotinic acid with one of the bases of the vitamin. R. R. Williams [481, 513, etc.,] repeated Funk's attempts to obtain the vitamin in a pure state ; but the only pure product he succeeded in isolating from Funk's vitamin mixture with a melting-point 233° C. was, once again, nicotinic acid. He then began experimental dosage with kindred substances. Pure trigonellin (methylbetain of nicotinic acid), p-oxynicotinic acid and nicotinic-acid-nicotine-ester gave quite indefinite results. Somewhat better curative results followed the administration of ill-defined condensation products of oxynicotinic acid with phosphoric pentoxide or acetic anhydride. As far as any antineuritic influence could be ascribed to

β-oxypyridin, α-methoxypyridin, α-methylpyridon, trigonellin, nicotinic acid, and betain, this was manifestly associated with the presence of a betain group in the preparation, so that Williams was inclined to believe that some such group must exist in vitamin. In further experiments, a definite improvement in the paralytic symptoms of pigeons suffering from polyneuritis was secured by α-oxypyridin and by 2-, 4-, 6-, and 2-, 3-, and 4-trioxypyridin. Inactive were nicotinic acid, cinchomeronic acid, chinolinic acid, 6-oxynicotinic acid, citrazinic acid, glutazin, and the anhydrides of 2-, 4-, and 6-trioxypyridin and tetraoxypyridin. Williams went on to make an observation which is likely to be of great importance in the further study of vitamins. He found that the effective substances lost their efficacy very soon after they had been prepared. He inferred from this that these substances, on keeping, underwent a metamorphosis from the active form into a tautomeric inactive form. He was, indeed, able to prove that α-oxypyridin exists in two keto-forms and one enol-form, and that only one of these three, the keto-form which crystallises in needles, has a marked antineuritic effect, the enol-form in particular being quite inactive. Similar relationships obtain in the case of β-oxypyridin γ-oxypyridin, γ-lutidin, and the anhydrides of methylpyridon, trigonellin, and betain. In the case of these substances, only the corresponding forms have a curative influence, and indeed the last three have no protective influence of any kind. The protective form seems to be a pseudobetain form, and it is a matter of the utmost importance that the animal organism is not competent to metamorphose the inactive form into the active form. Williams supposes that the leading characteristic of the vitamins must be a compound which in respect of its structure or of its energy-content is closely akin to such a pseudobetain ring. Compounds of this kind may form part of most of the simpler nitrogenous substances contained in the animal organs. Especially they may be present in the nuclein bases ; and it seems likely that Funk's vitamins owe their efficacy, in part at least, to some such pseudobetain form of nicotinic acid. Williams' account of the various forms of the oxypyridins was confirmed by Harden and Zilva, who, however, could not find that these

substances had any beneficial effect in cases of polyneuritis. Further researches must be undertaken before this problem will be ripe for a decision.

The investigations of Hofmeister, who found that the active preparations contained at least traces of impurities, and that the activity of these preparations disappeared when the purification was advanced a stage, seem to justify the supposition that vitamins are unstable substances which are capable of being preserved in a labile form as long as certain impurities are present, but undergo a metamorphosis into a stable form as soon as these impurities are removed. Hitherto we have paid too little attention to this possibility, which is likely to prove of decisive importance in the further study of the vitamins.

4. Occurrence of the Vitamins.

Vitamins are present in almost all anmial and vegetable substances used as food. In the animal body they are less abundantly stored in the muscles (which, when fresh, always contain a sufficiency) than in the parenchymatous organs. In plants we find them especially in the leaves and other green parts, that is especially in the vegetative organs ; whereas the parts used by the plants for storage, such as bulbs, tubers, and roots, contain them in less abundance. Still, the amount of vitamin in potatoes, for instance, is so large that even boiled potatoes are useful, not merely as a remedy, but also as a prophylactic. Fruit, too, in the kitchen sense of the term, is rich in vitamin, and so are seeds. Within the individual organs, the vitamin content of the various tissues differs greatly. Especially does this apply to seeds, whose endosperm contains so little vitamin that its use as an exclusive diet, or even as a predominant constituent of the diet, is the characteristic cause of beriberi. The germs of seeds are especially rich in vitamin. In like manner the vitamin content of eggs, which are the animal counterparts of seeds, is concentrated mainly in the yolk.

We can readily understand, therefore, how harmful it is when, in lands where bread forms the staple diet, the demands of a crazy standard of luxury should lead people to consume bread made only of endosperm. We have already learned that

in North America epidemics of beriberi have followed the use of such bread. We saw also that in 1911 the Japanese maintained that the spread of the railway system in their country must be responsible for the increase of beriberi along the new lines of communication. Since there had been no change in the mode of life of the Japanese peasants, these scientific authorities believed that the diffusion of an infective agent was responsible. But they overlooked the fact that, thanks to railway developments, the peasants had not merely acquired increased facilities for marketing their own agricultural produce, but had also become contaminated with the refinements of urban life, and had been provided with financial resources enabling them to buy polished rice milled in the towns and to abandon the use of the partially hulled rice formerly prepared in their own hand mills and foot mills. Willcox [1025] has shown that among the European troops in Mesopotamia during the recent war (men who were fed mainly on meat, and on bread made from the finest wheaten flour), epidemics of beriberi repeatedly occurred when circumstances made it necessary to replace the ration of fresh meat by tinned meat. The fine white flour contained extremely little vitamin, which was, however, sufficient when supplemented by the vitamin in fresh meat ; but when the meat had been sterilised by prolonged exposure to heat (probably the juices of the meat, and therewith the vitamins,[1383] had also been removed by pressure) the supply of vitamin was altogether inadequate.

Apart from these canning processes, the vitamin content of food can be so greatly reduced by excessive sterilisation or by some other faulty method of preparation (as by throwing away the water in which the food has been boiled) that it is no longer adequate to prevent the onset of polyneuritis. Over-roasting, likewise, can seriously reduce the vitamin content of meat, although the other vitamins in the diet will in general make good the deficiency. If, however, in such cases the amount of food taken be reduced owing to acute indigestion, or if the bodily requirement be increased by the onset of some febrile disorder, or the like, the vitamin content of the food may no longer suffice the needs of the weakened body, and there may ensue, if not beriberi, at least a more or less marked attack of polyneuritis. Such cases are

commoner than is generally supposed, especially in Europe, but owing to defective knowledge of their etiology they are apt to be confounded with other diseases.

Amongst the poorer classes of the population, such occurrences are fairly easy to interpret, but it is noteworthy that attacks of polyneuritis are by no means rare in Europe among well-to-do persons belonging to the cultured stratum of society. If in such instances we investigate the causes of the disease we shall usually find that the patient has recently had an acute gastric or intestinal disorder. He has thereupon been prescribed a very rigid diet, consisting of food that shall be easily digestible and simultaneously as "nourishing" as possible. In consequence of this the stomach and bowel have been increasingly disaccustomed from their proper tasks—the patient, who is usually a neurasthenic, paying sedulous attention to the behaviour of his body all the while. He thus gradually comes to believe that his system can only tolerate this or that food, and he adopts a diet which, even among persons to whom expense is no object, may be almost inconceivably restricted in respect of quality. Avitaminosis of all kinds may ensue in such patients, varying according to the nature of the diet and of the primary acute disease.

5. The Consequences of an Insufficiency of Vitamin.

a. Clinical.

If we are enquiring into the importance of vitamins to life, we can approach the question most effectively on the negative side by studying the consequences of a lack of vitamin. An account of typical beriberi can be found in every textbook of medicine, so that here I need merely summarise the cardinal symptoms. The manifestations of this disease are manifold and changeable, so that certain observers deny the unity of the cases commonly classed as beriberi, regarding them as polyneuritis complicated with some other illness, usually scurvy or oedema. In most instances the outbreak of the disease is preceded by general emaciation and loss of weight. The slighter form, called by some the sensori-motor and by others the latent form, begins with general symptoms, such

as minor digestive troubles, disinclination for work, and a proneness to excessive fatigue. By degrees, weakness in the legs and unsteadiness of gait appear. Paraesthesia is noticed in the nerves of the lower extremities, and circumscribed anaesthetic areas can usually be discovered in various parts of the skin below the knee. The knee-jerks, which are apt to be somewhat exaggerated in the initial stage, are by now generally absent. Commencing circulatory weakness is shown by slight and transient oedema and by occasional attacks of palpitation. In this condition, the illness may persist for years, the symptoms sometimes remitting or even almost entirely disappearing, to become accentuated at other times, especially in spring and autumn, or when unusual claims are made on body or mind. Acute intercurrent disorders, exhausting bodily exercise, or great mental excitement, may cause a sudden or gradual exacerbation of the beforementioned symptoms, and the same may result from a change for the worse in the diet.

There are great differences of opinion regarding the classification of the acute forms of the malady. Almost every investigator with practical experience of beriberi has his own classification, and this is perhaps the best proof of the multiformity of the disease. The only certain indication of its presence is the occurrence of the pareses, which may gradually pass into severe and extensive paralyses. The pareses usually begin in the toes and gradually spread upwards ; ultimately they appear in the upper extremities, beginning in the finger-tips, and exhibiting as in the legs a centripetal progression. Experimental polyneuritis displays similar characteristics, for in this, too, the pareses begin distally—in the feet of birds and in the hind legs of mammals—gradually spreading towards the centre. In experimental polyneuritis, likewise, there is what may be called a latent form, in which there are no definite pareses, but in which the clinical picture of ordinary marasmus is manifestly characterised by a certain awkwardness of movement on the part of the animal affected, just as in the precursory stage of beriberi in human beings.

We can also note marked tenderness in the affected muscles, with the formation of hard lumps in them (local tetanus),

disappearance of the patellar reflexes, extensive hyperaesthesia of the skin, and severe paraesthesias of various kinds, these symptoms indicating grave disorders of muscle and nerve. Only in the later stages do we find complete anaesthesia and reaction of degeneration. Intelligence is unimpaired to the last, although fits of depression are frequent, and where predisposition exists even mental disturbance may ensue. The later stages are always attended by profound apathy.

b. Pathological Anatomy.

If we examine the nerves in human beings that have died of beriberi and in animals that have succumbed from polyneuritis, we usually find marked degeneration of the finest nerve endings—a degeneration gradually spreading towards the centre, and ultimately showing itself in the spinal cord and even in the brain. In the peripheral nerves, the changes consist of degeneration of the medullary sheaths, and of degeneration and subsequent complete destruction of the axis cylinders, until in the end the latter are completely replaced by nucleated neuroplasma cylinders, which Dürck regards as a nervous matrix tissue. This view is doubtless correct, for even though complete restoration of the nerves may take a long time, the administration of vitamin will reestablish nervous functioning in a marvellously short period. Moreover, we frequently find extensive degeneration in nerves supplying muscles that have been working quite satisfactorily.

The next most striking feature to the pathologist is the atrophy of the muscles in the affected parts of the body, in which sometimes a typical myositis can be noted. The atrophy is distinguished from the ordinary atrophy of inanition by definite signs of degeneration : the cross-striation is obscured ; the sarcolemma sheaths have often burst ; their contents are softened, contain fat-droplets, and have here and there exuded from the sheaths. The nuclei of the muscle cells are markedly increased in number.

Similar conditions are observable in severe attacks of neuritis due to other causes, and notably in those dependent on intoxication. Hence it has been widely believed that the disease must be a primary polyneuritis due to intoxication.

Nocht,[74] however, pointed out as long ago as 1908 that there are certain fundamental differences between the degeneration typical of toxic neuritis and that typical of beriberi, and he therefore considered that the nerve degeneration of the latter must be regarded as purely atrophic. This theory is supported, above all, by the fact that even in the nerve bundles that are most gravely affected, certain fibres still appear intact, whereas in toxic degeneration all the fibres of a nerve are simultaneously affected.

Medical observers in general are of opinion that the nerve degeneration is the primary lesion, and that the atrophy of the muscles is merely a consequence of this. In my opinion, there are important grounds against such a conclusion. First of all, atrophy of the muscles, with subsequent degeneration of the muscular fibres, frequently occurs before there is any visible lesion in the nerves; and, secondly, the nerve lesions are not proportional to the severity of the pareses or paralyses. It is true that Köninger[7] maintained in 1884 that the nerve lesions were primary, and that the typical symptoms of the disease did not appear until after the onset of the nerve lesions. Vedder and Clark,[238, 307] again, who studied the lesions in the brain, deny the peripheral nature of the disease, and consider that the primary source of the symptoms is in the central nervous system. But these same observers, and also Eijkman, Cooper,[311] and Schaumann,[310] have repeatedly insisted that there is no demonstrable connection between the intensity of the paralysis and the degree of nerve degeneration. Attentive study of published cases shows that there have been many in which severe pareses or complete paralyses occurred, cases which proved fatal, without there being any nerve lesions discoverable on post-mortem examination; or at most there was a degeneration of the medullary sheaths, but in cross-section of the nerves no degeneration of the fibres could be detected. On the other hand, cases are frequently encountered in which the nerve lesions are most extensive, so that hardly a single healthy fibre can be detected even in the big nerve trunks, and yet before death no paralyses have been noticed and hardly even slight pareses.

c. The Forms of the Disease.

We must infer from these considerations that we are concerned, not with conditions that bear a causal relationship one to the other, but with parallel manifestations of a common cause. The pareses and paralyses are obviously not a consequence of the nerve lesions ; or, at any rate, are not necessarily so, for they can just as well be explained as the outcome of a primary affection of the muscles. Indeed, some have attempted to argue that the nerve degenerations, when these are slight, are a consequence of the degeneration and the putting out of action of the muscles supplied by the affected nerves.

The most probable explanation is that the nerves and the muscles degenerate and atrophy more or less simultaneously owing to some defect in nutrition. This theory is supported by the fact that the disease is always introduced by a marked falling off in weight, and we have already learned that both the nitrogenous balance and the total-ash balance are negative long before the outbreak of the illness.

In association with cases of beriberi of the type we have been describing, known as *dry* beriberi, we frequently encounter instances of the so-called *wet* beriberi, cases characterised by oedema. The oedema, like the pareses, appears distally, spreading upwards from the toes or from the finger-tips. Gradually the entire lower extremities are invaded, then the lower part of the trunk, then the thorax and the neck, until ultimately the face may be so much swollen that the features become unrecognisable ; hydropericardium, too, is exceedingly common. In this form of the disease, there is usually cardiac dilatation without valvular lesions and without hypertrophy. The pulse is regular, but feeble and frequent. In prolonged and severe cases, when the heart is overworked, there may be actual insufficiency at the dilated cardiac orifices, and murmurs may become audible. The urine is always greatly diminished, rich in urates, but usually free from albumin and casts, this showing that there is no renal irritation. In wet beriberi, the muscular atrophy is necessarily masked by the dropsy, and even the pareses may be more or less obscured. If, however, by rest in bed and

suitable diet, the dropsy be relieved, it becomes plain that muscular atrophy is present in such cases also. When the treatment is successful, there is an enormous discharge of urine, the oedema disappears with marvellous rapidity, and the patient now presents the typical picture of atrophic beriberi.

Sometimes we encounter a third type of beriberi, which should really be regarded as an aggravated form of dropsical beriberi. Whereas the normal course both of atrophic and of dropsical beriberi is chronic, so that the cases sometimes last for years, the *acute cardiac* form of beriberi is very rapid in its onset, and may even terminate fatally in a few hours from heart weakness. The exciting cause is, as a rule, some sudden demand upon the energies, as through very unusual bodily or mental exertion, the onset of an acute disease, or a major operation. There promptly ensues a feeling of serious illness, with extreme precordial anxiety, greatly increased frequency of the breathing (which is convulsive and anxious), marked cyanosis, violent retching, and sometimes haematemesis. The temperature is usually normal, the pulse is full but compressible and extremely frequent, with a lowered blood pressure; the heartbeat is violent, conveying a shock along the great bloodvessels. A natural consequence of this condition of the circulation is a marked reduction in the urinary excretion, culminating in suppression of urine and the onset of widespread oedema. Death takes place in collapse, with diaphragmatic paralysis, pulmonary oedema, a galloping pulse, and in many cases a clouding of the intelligence; in some instances, death takes place in coma.

If we wish to analyse the etiology of beriberi, we have to reckon with three main groups of symptoms. Most characteristic, in my opinion, are the atrophy and degeneration of the muscles, leading to the pareses or paralyses. Secondly we have to consider the nerve degeneration, which we shall incline to regard as a contributory cause of the paralytic symptoms only when the nerve degeneration is strongly developed—unless, indeed, we accept the view of many authorities who hold that the pathogenic factors give rise to a disorder of nervous functioning long before any anatomical changes have taken place. It seems to me difficult to credit the existence of such a functional disorder, seeing that the

reports of experimentalists repeatedly mention that the conductive power of the nerves for stimuli was retained. The third group of symptoms comprises the cardiac weakness and the onset of oedema.

6. Analysis of the morbid Manifestations.

a. Significance of the Symptoms.

In the previous section we have learned that these three groups of symptoms may occur almost independently each of the other, although muscular degeneration appears to be a constant feature of beriberi. It is invariably present, also, in the polyneuritis artifically induced by an ill-balanced diet, but this form of the disease is almost always characterised by the presence of more or less oedema. Some investigators affirm that the following three types can be distinguished among cases of polyneuritis: simple neuritis; neuritis accompanied by general enfeeblement; and extremely acute polyneuritis without neuritis properly speaking but characterised by grave debility. As regards the first of these, which is rare, I cannot help suspecting that atrophy is really present, but is masked by the oedema. For in experimental polyneuritis, also, we invariably find that the other symptoms do not appear until great bodily wasting has occurred, amounting to from 23 % to 30 % of the weight. Many authors have been disposed to refer this wasting to a loss of appetite in animals kept upon an ill-balanced diet. In answer to this contention, it has repeatedly been shown that the loss of weight usually begins directly the experimental animal is put on the pathogenic diet, and may be considerable before there have been any signs of a loss of appetite. Even when Chamberlain, Bloombergh, and Kilbourne [145] had recourse to forced feeding (cramming), they found that the onset of polyneuritis was always preceded by a loss of weight amounting to at least 21 %. It is true that in Fraser and Stanton's experiment, in which forced feeding of pigeons with polished rice was practised,[108] the weight of the birds remained almost constant—with the result, we may parenthetically remark, that the onset of polyneuritis was speedier than ever. No post-mortem examination appears to have been made in

these interesting cases, but it seems not unlikely that the body-weight was maintained, partly through oedema, and partly through the putting on of fat, although grave muscular degeneration may have ensued. However this may be, the conditions were so exceptional that Fraser and Stanton's experiment cannot help us to decide the problems of etiology in the absence of post-mortem examination.

The occurrence of oedema in beriberi is a secondary symptom, one which has nothing to do with the essential disease. The eighth chapter of this work is devoted to malnutritional oedema, and in that chapter we shall have to refer once more to the onset of oedema in cases of beriberi. We certainly have to do here, with an intercurrent affection, and are reminded of the frequent associtaion of beriberi with scurvy.

If the muscle degenerations and the nerve degenerations are to be regarded as parallel symptoms running an independent course, we may perhaps assume that our food contains two classes of vitamins, the absence of one of these giving rise to the nerve lesions, and the absence of the other giving rise to the muscle lesions. There is much evidence in support of such an assumption, a notable point being that most authorities incline to assume the existence of two distinct classes of vitamins. However, these respective classes seem to have different effects from those we might expect in accordance with the foregoing assumption. To clear up the matter, a more detailed examination of the data contained in the literature of the subject must now be undertaken.

First of all it is necessary to bear in mind the unanimous testimony of authorities that a natural nutrient, in so far as it is active at all, does not merely cure this or that symptom of beriberi or experimental polyneuritis, but relieves the entire syndrome. In beriberi, for instance, it does not matter whether we give rice bran, beans, or green vegetables, all of which are very active remedies, or whether we give one of the less powerful agents, such as milk. Provided the dosage of the remedial food be sufficient, a complete cure promptly ensues. But the results are very different when for curative purposes we use *extracts* made from the remedial nutrients and Schaumann [361] emphasises the assertion that the qualita-

tive no less than the quantitative effect of such extracts is less in proportion as the purification of the substance has been more thorough. Vedder [314] points out that crude vitamins employed as antineuritic remedies are from 20 to 30 times less effective than the foods from which they were originally derived containing the same amounts of these substances. *At the same time, the universality of effect has disappeared from the extracted crude vitamins, and each of these has an effect peculiar to itself.*

That is why so many authorities [284, 375, 516, 619, 666, 683, 691, 731, 874, 1040, 1066, etc.] have come to consider that at least two vitamins are indispensable for a cure. We may recall the observation of Funk [273] that the bases he isolated from rice bran and from yeast respectively were inactive when used separately, but were able to cure the paralyses when administered simultaneously.

b. Effects of Funk's Vitamins.

Certain investigators regard the vitamins as active remedies Thus, according to an early paper by Funk,[375] they definitely cure experimental polyneuritis in animals; Segawa [313] expresses the same opinion. The latter, however, noticed that the marasmus attendant on these cases was not relieved by the vitamins, and this led him to regard the marasmus as a secondary symptom, an outcome of the malnutrition consequent on the lack of balance of the diet. We have already seen that there are numerous indications against any such theory. Marasmus is not a secondary symptom in these cases; it is the first and most fundamental symptom. Pareses and paralyses are superadded as further characteristics. Marasmus and the nervous symptoms taken together combine to form the typical picture of beriberi.

In 1911, lecturing in Berlin, Schaumann for the first time recounted the experimental evidence to prove the almost miraculously beneficial effect of vitamins in pigeons paralysed by polyneuritis. But this cautious investigator pointed out that the birds' restoration to health was apparent merely. He said that rice bran must contain other substances which had to be given in addition to the vitamins if a real cure was to be effected. In default of these, the animal would die

notwithstanding the relief of the paralyses. About a year later, Strong and Crowell [223] reported that when experimental animals were fed on polished rice, the addition of alcoholic extract of rice bran to the diet sufficed to prevent the onset of paralyses; and that in animals suffering from experimental polyneuritis the extract would dispel paralytic manifestations, even when severe, within a few hours or days; but the administration of the extract did not prevent the death of the experimental animals. Vedder and Clark [238, 307] found that alcoholic extract of rice bran gave relief only in the fulminant form of polyneuritis, being then competent to remove the paralytic symptoms. Later, Vedder and Williams [284] noted that the different symptoms of beriberi required different vitamins for their cure. The Funk's vitamins precipitable by phospho-tungstic acid relieved the paralytic symptoms, and these only; on the other hand, the filtrate after precipitation by phospho-tungstic acid was useless for polyneuritic paralysis, but had an unmistakably beneficial influence upon the atrophy. In his important paper of 1914, Schaumann again and again insists that Funk's vitamins are only of use to relieve the paralytic symptoms, whereas alcoholic extracts of bran exert a complete prophylactic and curative influence.

Even more effective than alcoholic extracts of the bran, are extracts of rice bran made with water or with weakly acidulated water. Besides promptly relieving the paretic and paralytic symptoms, such extracts bring about marked improvement in the general condition, and lead to an increase in weight though not to a complete return to the normal.[361] An extract of yeast similarly prepared with water containing 0·3 % of hydrochloric acid acts in the same way, but far more powerfully. If yeast, after removal of the fat, is first hydrolysed with 10 % sulphuric acid and then extracted with water, the resulting extract is found by Schaumann [361] to be peculiarly efficacious against the paralytic symptoms, both as curative and prophylactic, but it is not otherwise valuable. In like manner, extracts made from katjang-idjo beans after predigestion with pepsin and hydrochloric acid are useless to prevent loss of weight and emaciation though active against pareses and paralyses. According to Voegtlin and Towles,[265] a watery extract of the spinal cord of

the ox was effective only against the paralytic symptoms. Vedder [307] noticed that insufficient supplies of vitamin can retard the onset of pareses and paralyses, but do not prevent loss of weight and emaciation; the period of incubation may be prolonged to as much as a year; when death comes at last, it is usually sudden. Schaumann [361] had the same experience. Adding inadequate quantities of alcoholic extract of yeast to a diet of polished rice, he found that the onset of pareses was thereby retarded, and yet the loss of weight was greater than in control animals fed on polished rice unsupplemented. Still, the animals receiving the yeast extract lived longer, and (except for the loss of weight) apparently in good health—until suddenly grave paralysis supervened, and death soon followed.

c. Differences between the Effect of Funk's Vitamin and that of water-soluble B or that of water-soluble D.

Williams and Seidell [560] report some interesting observations. In animals fed on polished rice, the fuller's-earth absorbate from autolysed yeast was administered; thereupon the paralytic symptoms disappeared, and concomitantly there was a notable improvement in the general condition. If the absorbate, before being added to the food, was treated with dilute alkali, it ceased to affect the general condition, though it was still competent to relieve the paralyses. In the original autolysate of yeast (before the fuller's-earth absorbate had been prepared from it) the effect of alkalies was the opposite; if the autolysate was allowed to remain in an alkaline solution for a considerable period, the effectiveness against the paralyses as a prophylactic and a curative disappeared, but the solution continued to bring about notable improvement in the general condition of the animals fed on polished rice. These observations have not been confirmed, but we know that vitamin is absorbed in a fairly pure state by fuller's earth; and since this absorption appears to be a physical reaction in which no decomposition of the vitamin need be expected to occur, we have theoretical grounds for supposing that the vitamin in this absorbate will really be pure. Now Emmet and McKim [666] have been able to prove that in pigeons suffering from polyneuritis the fuller's-earth

absorbate, though it relieves the paralytic symptoms, is quite without influence upon the loss of weight and the emaciation. These authorities therefore infer that the prophylaxis or cure of the marasmus requires the presence in the food of certain hitherto unknown substances, over and above the vitamins.

Sugiura [776] states that both the alcoholic extract of carrots and the crystalline substance prepared from yeast in accordance with his method have a powerful remedial influence in acute cases, as far as the paralytic symptoms are concerned, but do not relieve the marasmus; in chronic cases these preparations are of no use whatever. Weill and Mouriquand [731] likewise found vitamin effective in acute cases of paralysis only; in chronic cases of beriberi, more extensive pathological changes must have taken place, changes which vitamin could not influence. Abderhalden and Schaumann [803] expressly declare that the eutonins (see p. 22) rapidly and effectively relieve the nervous disturbances, but otherwise are devoid of beneficial influence; whereas rice bran and yeast (substances from which eutonins can be extracted), are strongly curative. It is interesting to note, moreover, that although an alcoholic extract of yeast [361] can relieve paralytic symptoms or prevent their onset, its administration tends to have unfavourable effect as regards the loss of body-weight. On the other hand, yeast which had been extracted with large quantities of alcohol—even four times in succession—was able to prevent or cure the disease, the loss of weight in these cases being only from 6 to 7 %.

McCollum and Simmonds [691] have been led by their researches to believe that only the nervous disturbances are referable to lack of vitamin. Hopkins and his collaborators [1066] come to the same conclusion.

We have quoted in this connexion no more than a few extracts from the literature of the subject. The reports of the other observers all have the same trend, and it is needless to cite them more copiously. Cooper,[269] whose experience was similar, attempted to ascertain the minimal quantities of a nutrient that must be given in order to prevent, in one series of cases paralytic symptoms, and in another series of cases loss of weight, on a diet of polished rice.

Fish was comparatively ineffective. Ten grammes of pike had no effect either on the paralyses or on the loss of weight.

Many investigators were, however, strongly disinclined to admit that there could be other vitally important substances in the food, substances still unknown to us. The presence of a fundamentally important substance in fat had been proved. This was absolutely distinguished from the anti-neuritic principle by its solubility in fat, and had therefore become known as fat-soluble A. Stepp [517] had given experimental proof that vitamin could not substitute fat-soluble A, and that the latter could not substitute the former. Since all the other essential substances were soluble in water, it

	Prevent Paralyses.		Prevent Loss of Weight.	
	Fresh.	Dried.	Fresh.	Dried.
	Grammes.	Grammes.	Grammes.	Grammes.
Bakers' yeast	2·5	2·5	2·5	0·5
Yolk of egg	3	1·5	10	5
Barley, decorticated ..	3·7	3·2	7·5	6·5
,, undecorticated ..	5	4·5	10	9
Bullock's heart	5	2	5	2
Sheep's brain	12	2·5	3 to 6	0·6 to 1·2
Lentils	15	3	30	6
Lean beef	20	5	20	5

was assumed that there was only one vitally essential water-soluble principle—vitamin. McCollum and his collaborators [490] were loath for a long time to tolerate the supposition that there are other unknown substances in the food which are indispensable to life and health. But inasmuch as McCollum's own work had shown beyond doubt that natural nutrients contain water-soluble substances essential to growth, American authorities did not hesitate to identify this growth-factor, this water-soluble B, with Funk's vitamin. The water-soluble antineuritic substances and the growth-factor did, in fact, react similarly in many respects towards heat and other agents, so that the assumption of their identity did not lack justification. Eddy [564] showed some years ago that, just like vitamin, the growth-factor could be absorbed from an extract of pancreas by Lloyd's prepared fuller's earth, and

could be precipitated by phospho-tungstic acid; and he proved that both preparations had an antineuritic influence. Drummond [619] arrived at similar results in his study of the antineuritic principle and the growth-factor in yeast, and he therefore came to the conclusion that the two substances were identical. Lecoq [1076] describes the growth-factor as soluble in water and alcohol, insoluble in fatty menstrua, resistant to acids, sensitive to alkalies, absorbable by colloidal aluminium oxyhydrate or iron oxyhydrate, and destroyed by prolonged heating at 120° C.

There was, consequently, considerable evidence in favour of the view taken by Drummond,[874] and by other British authorities [1194, 1554] as recently as 1922, that the water-soluble antineuritic principle and the complettin B are the same substance. But the objections to any such assumption are still stronger. As long ago as 1913, Funk [324] had shown that a diet may be rich in vitamin and nevertheless inadequate to promote growth and even to maintain body-weight. Abderhalden and Ewald [683] and also Abderhalden and Schaumann,[803] insist that the addition of extracts rich in vitamin to polished rice does not make of the latter an adequate food, whereas polished rice supplemented by a sufficiency of extract of rice bran is able to maintain life upon a normal footing. Hopkins [202] had shown as early as 1912 that whereas the various preparations of vitamin could not sustain growth, aqueous extracts of bran or yeast promoted normal growth

d. Differences between water-soluble B and water-soluble D

These results might be interpreted as showing that there is a distinction between vitamin and the growth-factor, but that the growth-factor is identical with the still unknown water-soluble substance which is essential in addition to the vitamins to the complete cure of beriberi and experimental polyneuritis. Bostock [316] assumes this identity as regards the active principles in rice, Byfield [1153] as regards those in orange juice, and Eddy and Stevenson [1205] as regards those in rice bran. Abderhalden [1040] had proved in the case of yeast that the antineuritic principle, in contradistinction to vitamin but in conformity with the growth-factor, was practically insoluble in alcohol. When, however, we carefully study such

researches as those of Osborne and Mendel concerning the complettin content of various parts of the wheat grain, a different result is reached. We have already learned that in this grain the antineuritic principle is concentrated in the germ, whereas the pericarp is somewhat less richly supplied than the germ, and the endosperm contains exceedingly little. According to Osborne and Mendel, however, in young rats loss of weight can be prevented when wheat germs are used as the only source of complettin, but in these circumstances growth does not occur. Although endosperm contains a smaller quantity of water-soluble complettins, when given in conjunction with the germs endosperm can sustain growth in rats. This observation can only be explained on the assumption that, as far as the growth-factor is concerned, the endosperm of the wheat grain must contain more than the germ. The water-soluble complettins in the germ must consist mainly of Funk's vitamins and the as yet unknown water-soluble antineuritic principle. In endosperm, on the other hand, there must be an adequate supply of the growth-factor, but Funk's vitamin and the antineuritic principle must be almost completely lacking.

An observation made by Sugiura and Benedict [980] can be similarly explained. A diet of bananas and casein is adequate for the maintenance of lactating rats, especially if supplemented by the antineuritic principle in the form of yeast added to the food to the amount of 0·5 %. But the milk secreted in such a diet does not sustain growth in the sucklings. The trouble cannot be ascribed to the protein, inasmuch as we have learned from other experiments that banana protein is rendered adequate by the addition of casein. Nor can the defect in the diet arise from a deficiency of inorganic nutrients; for the abundant supply of bananas is a guarantee that the food will contain an excess of bases, and although there may be a partial lack of calcium salts, these could be adequately supplied from the osseous system of the mother rat. The observers found that in these cases the addition of 0·5 % of protein-free milk rendered an adequate production of milk possible, and they therefore assumed that the milk thus added must contain some organic substance essential to growth which had been wholly or partially lacking in the unsupple-

mented diet. This substance could not be the antineuritic principle, for there was an abundance of that in the yeast. It would, of course, be possible to suppose that the antineuritic principle is able when administered in comparatively small quantities to prevent polyneuritis and to guard against loss of weight, but that in order to secure normal growth larger quantities are requisite than can be supplied by the amount of yeast actually given. On that theory, the requisite supplement of antineuritic principle had been furnished by the protein-free milk. We shall see, however, in a moment that this plausible interpretation is untenable. The experiments of Osborne and Mendel [1131] have, in fact, shown that yeast also contains the growth-factor, so that when the supply of milk is inadequate, normal growth can be sustained through supplementing it with small doses of yeast.

Loeb and Northrop [569] found that the growth-factor in the yeast was far more thermostable than the antineuritic principle; but whereas the latter was resistant to alcohol, the former was destroyed by it. However, this observation was made on the larvae of flies, and we are hardly justified in regarding it as convincing evidence in the case of higher animals. A fortiori this criticism applies to the researches of Emmet and Stockholm,[1203] Eddy and Stevenson,[1205] Miller,[1286] and Whipple,[1287] who used yeast as the test object in their experiments on growth; for subsequent investigations have shown that the modifications they observed in the growth of yeast were referable to numerous other factors, such as the provision of a better mixture of salts, the supply of carbohydrates, etc.

Nevertheless, the researches of Emmet and Luros,[1202] who fed pigeons and rats on unhulled rice, have shown clearly that there are differences between the water-soluble antineuritic principle and the growth-factor B. They found that the antineuritic principle can tolerate one hour's heating at 120° C. under a pressure of 15 lbs., but that it is partially destroyed by two hours in an air chamber at the same heat and pressure, and completely destroyed by two hours' exposure to the same heat at a higher pressure. In extracts, the antineuritic principle was even more sensitive to heat. The growth-factor, on the other hand, was not notably affected

by exposure to the same conditions. McCollum and Parsons [1300] were led subsequently to a different view, finding that when milk was boiled, the antineuritic principle was destroyed more rapidly than the growth-factor.

Funk and Macallum [563] tell us that the growth-factor is less stable and is more readily destroyed than the antineuritic principle in the process of purification by phospho-tungstic acid and silver precipitation. We can hardly accept this as a proof that the two substances are distinct, seeing that the method is obviously unsuitable for the isolation of the growth-factor. The method is the one employed by Funk for the isolation of vitamin, and we may therefore presume that the terminal product is simply a vitamin containing growth-factor as an impurity. We are all the more justified in such a contention seeing that, on the one hand, Funk and Macallum themselves tell us that the terminal product is very like Funk's vitamins, and on the other hand other observers have proved that both the growth-factor and the antineuritic principle are merely obtained in small quantities as an accidental impurity through precipitation by phospho-tungstic acid.

More convincing, in my view, is the statement of Sugiura and Benedict [967] that the growth-factor is destroyed by exposure to radium, whereas the antineuritic principle, as we have previously learned (p. 120), is unaffected thereby. Very important, likewise, is the fact observed by Verzár and Bögel [1270] that when growth-factor is subcutaneously injected it has no effect on either the glandular secretions or the blood-pressure, whereas the antineuritic principle, as will subsequently be shown, has a specific influence on the glands.

Summarising all these considerations, we are led to endorse the view first expressed by Mitchell [979] that the vitamins, the water-soluble antineuritic substances, and the water-soluble growth-factors, form three distinct classes.

e. Behaviour of the Glands.

To complete the picture, we must give an account of the anatomical and physiological effects of a lack of vitamin and the supply of vitamin. In supplement of what has already been said it should be mentioned that Funk has found changes in the brain. In cases of polyneuritis, the brain contains

considerably less nitrogen and 20 % less phosphorus than normal.[197] Schaumann points out that the glands, no less than the muscles, undergo gradual atrophy. Portier,[1103] van Driel,[1139] and Bierry, Portier, and Randoin,[1197] report, in conformity with numerous other observers, the same facts. When there is a lack of vitamin, there occurs atrophy of the testicles, spleen, ovaries, pancreas, heart, liver, kidneys, stomach, thyroid, and brain, the onset being practically in the order named. In the glands, the parenchymatous tissue gradually disappears, being replaced by connective tissue; the spermatazoa vanish from the testicles. The secretion of saliva, gastric juice, pancreatic juice, bile, and intestinal juice, declines. In contrast with the other glands, the pituitary body and the adrenals become enlarged, but the secretion of adrenalin is greatly reduced, although the adrenals apparently contain more of this substance than usual.

The administration of vitamin rapidly changes the picture; the glands resume their secretory activities, and by degrees the atrophic changes disappear. In young animals, the testicles, even though they have degenerated so extensively that the active cells have been almost entirely replaced by connective tissue, return to the normal and produce spermatazoa once more.[1107] With the reappearance of the digestive secretions, the appetite, which has been in abeyance, returns, and is often ravenous. Extremely characteristic is an observation by Fletcher, quoted by Fraser and Stanton.[108] At the height of experimental polyneuritis, when pigeons refuse food and are forcibly fed, the rice remains unchanged in the distended crop. But if, now, a small quantity of rice polishings be introduced into the crop, the accumulated rice is speedily dissolved, and the normal powers of digestion return, with a revival of appetite. Uhlmann,[632, 755] using the commercial preparation known as orypan,[884] has made a detailed study of the effects of the administration of vitamin in birds and mammals suffering from experimental polyneuritis. In general, he found that vitamins have the same effect whether administered by mouth or by subcutaneous or intravenous injection. Above all, there is a powerful stimulation of the parasympathetically innervated glands, the action resembling (though not identical with) that of pilocarpin, muscarin, or

cholin, and similarly arrested by atropin. As particular effects, Uhlmann refers to increased secretion of nasal mucus, tears, sweat, saliva, gastric juice, bile, pancreatic juice, and intestinal juice; in respect of the last four secretions, his observations have been confirmed by Voegtlin and Myers,[921] and also by Willcox.[1036] According to Uhlmann, the stimulating influence on the pancreas is akin to that of secretin, though less powerful.

Willcox reports that the incretory activities of the glands are restored by the administration of vitamin, but I have not been able to find any mention of the effect upon the hypertrophied pituitary body and the adrenals. We are not told whether these remain enlarged, or return to their normal size.

The unstriated muscles, no less than the striated muscles, are powerfully stimulated by injections of vitamin. The action resembles that of injections of pilocarpin, muscarin, or cholin, and is similarly inhibited by small doses of atropin. On the heart, vitamin works by way of powerful vagal stimulation, and the enhanced vigour of the organ is transmitted to the arteries in the form of a strong pulse. The arteries expand and the blood-pressure falls.

The fact that the pituitary body and the adrenals, in contradistinction to all the other glands, undergo hypertrophy, cannot fail to attract special attention. It is all the more remarkable, then, that in the whole literature of the subject no further reference should be made to this peculiar reaction of the pituitary body, although the reaction must manifestly be the expression of some special defensive measures on the part of the organism. The lack of vitamin must plainly have caused some sort of disturbance in the animal economy which demands exceptional activity from the pituitary body and the adrenals, and thus leads to their hypertrophy—at any rate we can imagine no other explanation. But we know nothing of the part played in the matter by the pituitary internal secretion, although the phenomena described challenge investigation. In the next chapter, when we come to study the growth-complettin, we shall learn that the pituitary body forms an internal secretion whose effects are in many respects similar to those of complettin B, and whose function may possibly be to increase the activity of the internal respiration

of the tissues. It is perhaps because the active principle has not yet been isolated with certainty, that we know so little concerning the part played by the pituitary body in relation to polyneuritis. We are still uncertain whether the substance known as tethelin (infra p. 202) prepared by Robertson and Ray from the anterior lobe of the pituitary body is the real active principle, and possesses the chemical composition ascribed to it.

Conditions are very different as regards the adrenals. We know with certainty that each of the two parts of the gland produces a well-defined substance. From the medullary cells come adrenalin, which contracts the blood-vessels and raises blood-pressure; and from the cortical cells comes cholin, whose effects are the opposite of these. By the reciprocal activities of the two substances, the blood-pressure is maintained at its normal level. In the disease we are considering the hypertrophy of the adrenals mainly affects the medulla, whereas the cortex of the gland inclines towards atrophy. Many investigators have therefore been led to infer that an increased formation of adrenalin takes place in beriberi. McCarrison [1215] explains the occurrence of oedema in cases of polyneuritis as follows. He supposes that owing to the excessive supply of adrenalin the small bloodvessels are strongly contracted, and that by the consequently increased blood-pressure the blood-serum is forced through the walls of the vessels and infiltrates the tissues. Barr [1055] has, however, pointed out that, whilst the contraction of the arterioles caused by adrenalin does indeed lead to an increase of pressure in the arteries, in the arterioles themselves and in the capillaries, the pressure is lowered and the blood-stream accelerated. The effect of adrenalin must, therefore, be to hinder the onset of oedema. Moreover, it has been proved that in polyneuritis the blood-pressure is diminished rather than increased, so that we must assume the existence of a vasomotor paresis. But the fall in arterial pressure due to relaxation of the arterioles is attended by an increased capillary pressure, favouring transudation and the consequent onset of oedema. McCarrison has, therefore, formally withdrawn his hypothesis.[1055]

Cramer [1251, 1253] comes to another view, which is certainly

better founded. He assumes that the internal secretion of the adrenals is, like that of all other glands, reduced by a deficiency of vitamin. The hypertrophy is to be explained as an outcome of the attempts of the adrenal to keep up the supply of adrenalin, a substance essential to life. The vitamins requisite for this are obtained by the liquidation of material from other glands of less vital importance. Ultimately, of course, the supply of vitamin from these sources is exhausted, and then no more adrenalin can be produced notwithstanding the hypertrophy of the adrenals.

The hypothesis is strongly supported by the behaviour of the body temperature in beriberi and experimental polyneuritis. The temperature falls, though very slowly, and this may be interpreted as a sign of the reduced formation of adrenalin. Suddenly, just before the end, the temperature falls by as much as 3° C., and death thereupon ensues. In normal circumstances, the body makes an effective response to a fall in temperature by the increased formation of adrenalin, and we may therefore infer that the sudden fall in temperature at the close of the illness is due to a failure in the formation of adrenalin. In conformity with this theory we find that, whereas during the general course of the disease the adrenalin content of the adrenals is found to be normal, or even somewhat increased,[1030, 1197, 1215] when the collapse of temperature occurs just before death there is a sudden decline in the adrenalin content of the adrenals.

f. The Energetics of the muscular System.

We have now come to what may perhaps be regarded as the most important chapter in the pathology of polyneuritis, to the question of the energetics of the muscular system. It has long been known that there is a gradual fall in temperature in polyneuritis, and Dutcher[994] has recently provided experimental confirmation of the fact. Raimono,[478] too, showed in 1916 that the respiratory quotient slowly declines, ultimately reaching a level which is barely half the normal. This observation has been confirmed by Tanji.[745] In conformity therewith, study of isolated muscle has shown a marked falling off in the internal respiration of the tissues. Abderhalden,[1255] whose observations show that extracts rich in vitamin

promptly restore tissue respiration to the normal, is of opinion that the substances he terms nutramins act after the manner of co-enzymes, inducing conditions which direct tissue respiration and the other activities of the cells into normal channels. Freudenberg and György [1281] have also been able to show that numerous vegetable extracts, and also codliver oil, linseed oil, and cream, must contain substances able to increase the respiratory activities of animal cells.

It is, however, necessary to note that the previously described behaviour of the muscular tissue is by no means peculiarly characteristic of polyneuritis. Abderhalden and Schmidt [1302] have detected a like decline in the energy of tissue respiration in all diseases attended with muscular atrophy, the change taking place only in the wasted muscles, and being discernible only when these are examined quite fresh. If the experiment was not made until after the muscle had been kept for from nine to twelve hours, it could not be shown that vitamin had any influence on tissue respiration

Even if Abderhalden's observations are accurate (and there is no reason to question them), the causal relationships may be entirely different in the various diseases. We may assume, for example, that in consequence of a febrile disorder the catalase content of the tissues has been used up, and that thereby a weakening of the muscles has ensued, leading to atrophic changes in these organs. Naturally in such cases tissue respiration will be rendered more active as soon as catalase is produced once more thanks to the effect of vitamin. We might, on the other hand, accept the prevailing view that the nerve lesions are primary, and that the muscular atrophy is a secondary change. But in that case it would be difficult to see why tissue respiration should become less active as long as there is an adequate supply of blood, for the primary nerve disorder could not easily affect the catalase content of the muscles. The conditions are different if we assume the muscular degeneration to be a primary lesion dependent upon the absence of the co-enzyme vitamin. In that case, it is natural that the activity of tissue respiration should gradually decline in proportion as the co-enzyme disappears from the muscles, although the catalase content of these may be unaffected, and the catalase is ready to be restored to activity

as soon as vitamin is supplied. But even this theory does not touch the root of the matter. The researches of Eijkman and Hulshoff-Pol, and also those of Dutcher,[753, 994] have shown that in polyneuritis the catalase content of the muscles is by no means unaffected, but rapidly declines, ultimately falling to barely half the normal. Dutcher's work, and especially that done by him in collaboration with Collatz,[797] has shown that the administration of vitamin restores the influence of catalase, not because (as Abderhalden assumes) catalase already present in the muscles is activated by the vitamin, but because under the influence of the vitamin a new formation of the absent catalase takes place.

g. Differences between Polyneuritis and starvation States.

There is no doubt a resemblance in the condition of the muscular system in beriberi and experimental polyneuritis as compared with that in other diseases leading to emaciation. More especially, the energetics of the body are closely akin in beriberi and polyneuritis to what obtains in simple starvation. There are, however, important differences between the economics of the maintenance of bodily heat in simple starvation and in avitaminosis, respectively, as we learn from the admirable studies of Novaro.[1048, 1110, 1126] The importance of the matter justifies its detailed discussion. In both cases, three periods can be distinguished: an initial stage, which lasts one or two days in starvation, but a fortnight or more in avitaminosis; then comes a long intermediate stage; this is succeeded in both cases by a brief final stage culminating in death.

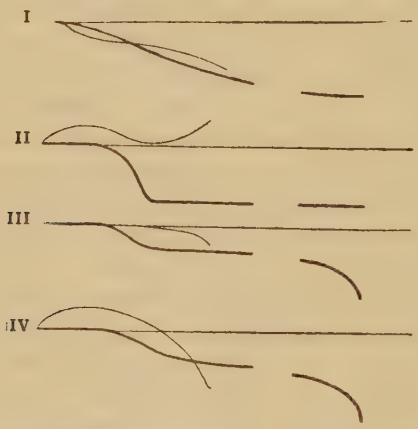
In simple starvation (in pigeons) the daily loss of weight during the initial stage ranges from 4 % to 7 % per diem; in the intermediate stage, the loss does not exceed 2 % or 3 % daily; in the final stage, it rises once more to the same level as in the initial stage. Both in the initial and in the final stage, the daily loss of heat is considerably greater than in the intermediate stage. At first the body temperature is unaffected, then a gradual decline sets in, and in the final stage there is a sudden fall. We see, then, that the fall in temperature does not run parallel with the loss of heat; the temperature may be almost normal even when the loss of

heat is from 50 % to 60 % above normal. If follows that during the initial stage the production of heat must be considerably greater than normal, but that a decline in heat production must gradually set in ; ultimately the heat production falls off so much that it is barely possible to keep the body temperature high enough for the maintenance of life, until at last the balance between production and loss is so greatly disturbed as to induce the catastrophic fall in temperature that immediately precedes the fatal issue.

In the avitaminoses, however, the temperature and the loss of heat remain normal for a time. The body-weight gradually declines, the decline becoming rapid after a while, in conjunction with a commencing failure to absorb nutriment. The weight falls off far more rapidly than in simple starvation, and subsides to a much lower level. The loss of heat is much reduced during the intermediate stage, until after three or four days the loss amounts to only about half the normal ; thenceforward the loss continues at this rate even in the final stage. The temperature, which (in pigeons) is normally 42·2° C., sinks rather rapidly to 41° at the outset of the intermediate stage, but thereafter the decline is slow, so that at the end of the intermediate stage it is still as high as 40°. When the final stage sets in, the temperature falls rapidly to about 37°, when death ensues. It follows that at the outset of the intermediate stage the production of heat must be considerable ; thenceforward, heat production must slowly decline and in contradistinction to what happens during starvation it must permanently be less than normal. Moreover, the collapse in temperature at the close does not depend (as in starvation) upon increased loss of heat, but upon a further sudden fall in, or perhaps an absolute arrest of, heat production.

When the experimental animal is put upon an adequate diet in time to save its life, the return to normal occurs in much the same way after prolonged starvation and after avitaminosis. It is true that after starvation the return of appetite is gradual, whereas when vitamin is given to an animal suffering from experimental polyneuritis, the creature becomes ravenous almost immediately. Still, the difference soon disappears, so that after a few days the quantity of food taken is in both cases about 50 % above normal. Not

until after the normal body-weight has been reattained does the taking of food become normal in amount. When the change for the better is made in the diet, the body-weight increases rapidly by from 10 % to 20 % ; then it remains stationary for a while ; thereafter a slow and somewhat irregular increase proceeds until the normal weight is regained The loss of heat also increases, though it remains for a time 5 % less than normal after starvation, and 20 % less than normal after a vitamin-free diet. Then the loss of heat gradually rises, and rises somewhat more quickly than the body-weight, so that, by the time the normal body-weight has



—— AVITAMINOSIS. —— STARVATION.

I. Body weight
II. Heat loss.
III. Body temperature.
IV. Heat production.

been regained, the loss of heat may be as much as 115 % above normal. Thereafter it gradually sinks to the normal. During the first twenty-four hours of recovery, the body temperature rises to about 41°, the rise being subsequently slower, until in four or five days the pigeon's normal temperature of 42·2° is regained. Thus the heat production is comparatively small during recuperation ; the food that is assimilated is mainly transformed into the tissue that replaces what has been lost, and is not used to any considerable extent for the supply of heat energy. Not until the bodily condition has become normal once more is an excess of heat production possible upon a food consumption that still remains excessive

for a time, so that an increased loss of heat is now manifest. When the appetite is once more normal, the food consumption also becomes normal, and heat production sinks to the ordinary level.

The curves in the figure give a graphic representation of the changes in avitaminosis and starvation respectively. The reader must note that, just as in the case of geographical relief contours, the vertical element in the curves is greatly exaggerated in comparison with the horizontal element, for were the vertical element represented in due proportion within the horizontal space available in such a figure, the vertical gradation would be hardly noticeable. The course of the weight curve suffices to show that in beriberi we cannot simply be concerned with malnutrition dependent upon an ill-balanced diet, but that there must be lacking in the food some constituent which normally renders its full utilisation possible, whereas in starvation there is a simple combustion of the body material without the possibility of any substitute ; that is why the curve in beriberi is far less steeply graded for a time, until the body's own supply of the requisite material is all consumed, whereupon a steeper gradation is shown. Inseparably connected with this is heat production. In starvation, the body must meet all its needs out of its own substance. Since the heating material thus available consists mainly of protein, and since protein cannot be adequately utilised for all the purposes of the body, there must be much wastage in this process, and the combustion of the waste materials leads to an increased heat production. But as soon as the fuel in the body runs short, the heat production suddenly declines, falling far below normal. In polyneuritis, the conditions are reversed. Here, there is a supply of mere fuel, and during the initial stage this fuel is utilised in a fairly normal fashion ; but as soon as the specific peculiarity of the disease, diminished faculty of utilisation, comes into play, heat production falls off in proportion to this lessened faculty for utilisation—very rapidly, at first, until the body has accommodated itself to circumstances, and then more slowly ; until at last a complete incapacity for utilising the food sets in, and heat production suddenly falls to a minimum.

The obverse of heat production is heat loss. In starvation

states the latter is always increased. At first the increase is due to increased heat production; subsequently heat loss still remains above normal, although heat production has now fallen below normal; finally, just before death, there is a renewed sudden rise in heat loss. In avitaminosis, heat loss runs a very different course. At first, like heat production, heat loss remains normal; then, when heat production is reduced, heat loss exhibits a sudden decline; and thence-forward it remains unchanged at a low level.

The body temperature depends upon the relationship between heat production and heat loss. In starvation states, heat production is, as we have seen, increased in the initial stages; but since heat loss is likewise increased, the temperature remains normal for a considerable period. Not until heat production is greatly reduced, so that it is no longer sufficient to compensate heat loss, does the body temperature undergo a gradual decline; in the final stage, when heat loss is very rapid and heat production has ceased, there is a collapse in the body temperature. In the avitaminoses, likewise, the temperature remains normal, here for the reason that at first heat production and heat loss are both unaffected. Subsequently, when heat production falls off, there is a marked regulative decline in heat loss, but the compensation is excessive, and a rather rapid fall in temperature results. In the final stage, when heat production ceases and heat loss continues, a sudden and fatal fall in temperature ensues.

The differences between the behaviour of the animal organism in starvation states and in the avitaminoses, respectively, is manifestly due in part to differences in the adrenalin production. At the outset of the starvation period, heat production is excessive, and the body temperature must therefore be regulated by a dilatation of the bloodvessels to permit increased heat loss, this involving no exceptional demand for adrenalin. Subsequently, when heat production declines, the normal tendency of the body is to react by increased production of adrenalin, in order to promote vascular contraction and thereby reduce heat loss. By this time, however, the adrenals have been so much injured by the starvation that the adrenalin production is inadequate. The temperature therefore falls, and the fall is more extensive in

proportion as the adrenal inadequacy is greater—until at last a critical collapse of temperature ensues.

In the avitaminoses, also, adrenalin production is obviously soon impaired, this resulting in a sudden fall of body temperature. However, as Bierry, Portier, and Randoin [1197] have shown, the body uses its last reserves of vitamin (perhaps secured by the liquidation of material from other glands) to maintain to the utmost the activity of the adrenals. The latter undergo hypertrophy in consequence of the increased demand made on their energies, but do not succeed in producing more adrenalin than is requisite to maintain the body temperature at the lower level to which it has now fallen. Ultimately the adrenals can no longer function. Perhaps there is no longer anywhere in the body vitamin-containing material available for liquidation. Another possibility is that heat production has become quite insufficient. Anyhow, a critical and fatal fall of temperature now ensues.

7. Earlier Attempts at Explanation.

These facts have additional implications, which will perhaps enable us to gain a more intimate understanding of the essential nature of the disease and of the way in which it comes into being. But before I turn to my own speculations concerning these problems, I must give an account of the views published by other observers anent the significance and the functions of the vitamins.

First let us consider the theories of Portier and his collaborators. They hold that the three stages of the disease are mainly determined by the vitamin provision of the body and its influence on adrenalin production. In the initial stage, the organism still possesses a store of vitamin adequate to supply the needs of all the glands. In the second stage, the vitamin content of the organism is no longer adequate, and the adrenalin production is falling off, but the latter trouble is more than compensated by the hypertrophy of the adrenals, so that in this stage the body actually contains an increased percentage of adrenalin. Thanks to the increase in the adrenalin content and the resulting persistently high tension of the vascular walls, there ultimately results the frequently observed sclerosis of the finest capillaries. In the third stage,

adrenalin production ceases entirely; there is, therefore, a catastrophic fall of body temperature; and death follows. This explanation, as we saw in the last section, makes due allowance for the changes in the body temperature; but it ignores the main causal factor of polyneuritic disorders, namely the atrophy and degeneration in the muscular and nervous systems. Furthermore, one of the fundamental assumptions of Portier's theory is in plain conflict with the facts. According to the theory, in the intermediate stage there should be a great rise in blood-pressure owing to the increased adrenalin production; as a matter of fact, during this stage blood-pressure is very low. However adequately the theory may seem to account for the changes in body temperature observed in polyneuritic disorders, it is so defective in other ways that it cannot be accepted even as a working hypothesis.

Another attempt to indicate the mode of action of the vitamins has been made by Häussler,[1245] who puts forward three alternative hypotheses. His first suggestion is that perhaps the glands participating in the work of nutrition cannot produce their secretions without the stimulus of vitamins. The second suggestion is that the vitamins may partake of the nature of ferments, and be able to accelerate the processes of intermediary metabolism. The third alternative is that the vitamins may be essential to the formation of hormones, so that hormones cannot be formed when vitamins are lacking. Häussler is well aware that these hypotheses do not take us very far, and he propounds them merely as accessory hypotheses. They are not even that, for they merely remove the questions to a new field without supplying any answer. It is indubitable that the glands are influenced by an adequate diet, but this does not explain how a paralysed pigeon is enabled to fly within a few hours of the administration of vitamin. The second hypothesis is even less helpful than the first, and perhaps the third hypothesis is in yet worse case, for (apart from the fact that the mechanism of ferment action, and also the formation, nature, and functioning of the hormones, are still a sealed book) neither of these hypotheses tells us anything regarding the place where the vitamins take effect or concerning their mode of action. Furthermore

while the hypotheses might explain either the symptoms of vitamin deficiency or else the positive effects of vitamins, they cannot explain both of these.

It is not possible to speak much more favourably of the assumption of Abderhalden,[1255] who believes that the vitamins, functioning as co-enzymes, must create conditions whereby tissue restoration and other cell processes are directed into normal channels. For although this theory indicates a point of attack and conveys some ideas regarding the mode of action, we have no evidence that catalase needs a co-enzyme to activate it. Nor does Abderhalden's theory explain why, in this disease, an insufficiency of catalase is formed in the muscles, or why, perhaps, catalase is not formed there at all.

By far the most notable attempt to explain the mode of action of the vitamins is that made by Schaumann,[73, 90, 122, 157, 173, 177, 219, 226, 310] and by Schaumann in conjunction with Abderhalden.[803] As long ago as 1904, Durham [44] showed that the excretion of phosphates is greatly diminished in beriberi. Schaumann was the first to point out that polished rice is very poor in phosphates as compared with unhulled or partially hulled rice. In the course of his further researches he found that poorness in phosphates was characteristic of all the nutrients inducing beriberi or experimental polyneuritis, and he was therefore inclined for a time to regard a deficiency of phosphates as the effective cause of the disease. Other investigators, such as Fraser and Stanton,[108] Aron and Hocson,[11] etc., made similar observations. But it became apparent, especially in the course of Schaumann's own work, that the addition of inorganic phosphates to a pathogenic diet had no good effect whatever, and Schaumann was therefore compelled to modify his theory that a deficiency of organic phosphorus compounds was of primary importance.

These were the days when lecithin therapy was still highly favoured; although the discovery of phytin had furnished lecithin with a powerful rival. In view of the scantiness of the chemical information possessed by most medical men, it was not surprising that people should have believed themselves to have discovered in these *mixed-organic* compounds the long and arduously sought *organic* phosphorus compounds.

But Schaumann's attempts with phytin and lecithin were no less fruitless than those with better defined phosphorus compounds. Only nucleinic acid, and especially the form derived from yeast, gave positive results, though the effect of these substances was far less powerful than that of extract of rice bran. When it was now discovered that Funk's vitamins were in fact devoid of phosphorus, Schaumann had to remodel his hypothesis again, and he assumed that the vitamins played a part in intermediate phosphorus metabolism, functioning as a kind of phosphatases. This seemed all the more plausible seeing that Schaumann's own comprehensive studies of metabolism as well as those of other investigators [247, etc.], had shown beyond dispute that in polyneuritic disorders the phosphorus balance is strongly negative despite the reduced excretion. It has subsequently appeared, however, that, even when Funk's vitamin is administered, and the power of voluntary movement is restored, the phosphorus balance remains negative, and this observation puts the last explanation out of court. But besides Schaumann (who not being a medical man, had to be guided in medical matters by the opinions of the faculty), all the leading medical authorities regarded the nervous paralysis as the primary lesion. Moreover, in the nervous system and in the glands there could be detected, not only an atrophic degeneration, but also a disturbance of the phosphorus metabolism which it was natural to regard as the cause of the failure of nervous functioning. From 1912 onwards, therefore, Schaumann inclined to regard the role of the vitamins in intermediate phosphorus metabolism as mainly one of activation. He therefore suggested for these substances the name of " activators," but subsequently withdrew the suggestion in deference to the priority of the name vitamin.

Tschirsch [1004] was doubtless influenced by Schaumann's researches in formulating the hypothesis that the cause of beriberi must be the incapacity of the body, in the absence of vitamins, to effect the cyclopoiesis that is requisite for the formation of the nucleoproteins. He thus regards the vitamins as ring-closing ferments, without whose aid the food cannot be utilised for the upbuilding of nucleoproteins. Apart from the fact that this theory does not provide any explanation

of the almost instantaneous restoration of mobility which ensues when animals suffering from experimental polyneuritis are dosed with vitamin, it cannot be taken as proved that the human organism is incompetent to effect cyclopoiesis, and that human beings would simply starve to death if the necessary ring compounds were not provided ready-made in their food. This attempt at explanation must, likewise, be rejected.

It is worth mentioning that in 1916 Voegtlin [586] endeavoured to explain the action of vitamins on the theory that they served to neutralise the toxins resulting from an excess of carbohydrates in the food and the consequent intestinal fermentation. Inasmuch as Voegtlin's own work contributed powerfully to promote a better knowledge of the mode of action of the vitamins, there can be no doubt that this authority spontaneously recognised the untenability of his hypothesis, for we find no further mention of it in his subsequent writings.

8. Summary.

I am not a medical practitioner, and the independent views I shall put forward in this section are therefore advocated with all reserve. In my opinion, however, there are certain facts which may guide us in our search for the causes of polyneuritic disorders. I have repeatedly insisted that the nerve degenerations cannot be the primary causes of the paralyses. For, first of all, the latter occur in cases where on post-mortem examination we can detect no nerve lesions. Secondly, even in the worst cases, the nerve degeneration is never complete, seeing that some fibres always remain in good condition. Thirdly, the restoration of mobility is an almost instantaneous affair, so that there is absolutely no time for the recovery of a damaged nerve. Finally, we learn from anatomical evidence that the general improvement is speedy, whereas nerve regeneration in the best event requires months. (Cf. Vedder and Clark,[238] and Schaumann [310].) For the same reasons, it is impossible to regard muscular degeneration or atrophy as the primary cause of the symptoms. The instantaneous restoration of the mobility of a degenerated muscle is as unthinkable as the instantaneous restoration of the conductivity of a degenerated nerve; and we have

learned that a definite interval must, in fact, elapse before the muscular system is fully restored to the normal.

It is therefore necessary to assume that, degenerative changes notwithstanding, the possibility of functioning is preserved should it be possible, either to remove an inhibition, or else to supply some substance that is lacking. An obvious assumption is that the vitamins are indispensable stimuli. It has been shown in the foregoing that similar effects to those produced by vitamins can to some extent be produced by well-known organic bases, although the influence of these is not lasting. An electric current, however, has similar effects, and we are certainly not entitled to contend that the absence of animal electricity is a cause of the paralyses, or that animal electricity is produced by vitamins. Similar effects are not always due to identical causes. In no science is the validity of this principle more conspicuous than in physiology.

Matters will perhaps be cleared up by a consideration of the general determinants of muscular movement. This movement is a manifestation of energy, and presupposes the prior existence of that energy. Now the motive power of the animal organism is combustion, and in animal life we cannot conceive any manifestation of energy in the absence of combustion. The formation of lactic acid and carbonic acid, products of combustion, during muscular movement, shows that oxidation is an essential determinant of such movement. If, therefore, we inhibit the combustion, no movement can take place even though the nerves and muscles are intact —unless energy be supplied from without, as for instance in the form of electricity.

In polyneuritic disorders, the combustion in the muscles is, as we have repeatedly learned, reduced. This defective combustion has been experimentally shown to be mainly due to the lack of a sufficiency of catalase. Experiment has likewise proved that the catalase content and therewith the tissue respiration, i.e. the possibility of combustion, is restored by the supply of vitamin. Finally, there is experimental evidence that what happens in the muscles in polyneuritis when vitamin is supplied is, not so much that already existent catalase is activated by the vitamin, but rather that *the provision of vitamin actually increases the catalase content of*

the muscles. In a word, the vitamin must lead to the new formation of catalase.

This, then, is the core of my theory. Under the influence of vitamin, the catalase content is kept at the requisite level. We must still leave open the problem whether the vitamins play an active part in the building up of catalase as necessary constituents of that substance, or whether they are to be regarded as directly operative catalase-forming ferments, or whether (as Abderhalden suggests) they represent co-enzymes essential to the formation of catalase.

This merely provides an explanation of the polyneuritic syndrome. The origin of the atrophy and degeneration of the muscles and nerves still remains to be explained, and here we must invoke the action of a substance of which we as yet know very little, the water-soluble antineuritic complettin, which for short I shall now call D.[388] It has been shown that Funk's vitamin, the real antineuritic principle, will relieve the paralytic manifestations, but only these, it does not cure the atrophy and degeneration of the muscles and the nerves; and death inevitably ensues in such cases even though Funk's vitamin be given, unless D be also added to the diet. Numerous attempts have been made to describe the symptoms as no more than the results of inanition. There are, doubtless, plenty of grounds for such an assumption. Recently, Simonnet [1301] pointed out that both in beriberi and in experimental polyneuritis the diet is extremely ill-balanced, and must certainly be inadequate in more respects than one. This authority errs as regards beriberi, for in that disease, though we speak of its origination by a rice diet, we do not usually imply that the patient has taken no food but rice. The diet may have been varied, but the mistake has been that the staple article of food has been polished rice. Moreover, beriberi broke out among the European troops in Mesopotamia, and the diet of these well-fed Englishmen must certainly have been a varied one. Underfeeding as regards protein, fat, inorganic salts in general, and also complettins A and C, may therefore be excluded as a cause of beriberi, and we must seek another etiological factor. We must certainly approve Simonnet's proposal that in future experiments a diet should be given that shall be fully adequate

except for the absence of the antineuritic factors, for we may hope in this way to secure clearer and more trustworthy clinical pictures. Hitherto these clinical pictures have often been confused by intercurrent disorders, especially by manifestations of the hæmorrhagic diathesis and by oedema, so that the disorder which was the primary object of study had been rendered almost unrecognisable. On the other hand an artificial diet such as Simonnet experimented with (meat thoroughly boiled and pressed, and subsequently extracted with alcohol and ether ; Osborne's salt mixture ; agar powder ; earthnut oil ; butter fat ; quantitative filter paper [as roughage —see below p. 190] ; potato starch ; and distilled water) will, indeed, be vitamin free, but is likely to contain D after all. In fact, in the diet named, there is D in the agar powder, the fats, and the potato starch. The result was that this diet rapidly induced severe paralytic symptoms with tetanic spasms, but the animals' loss of weight was much smaller than is seen in cases of beriberi, and the typical atrophic form never developed.

It would have been much better to retain the familiar experimental diet, supplementing it with specific substances —salts ; A, B, and C ; protein ; superheated fat.

Almost at the same date as Simonnet, Karr,[1293, 1294] made similar experiments which were invalidated by the same error and led to the same result. The main fault of Karr's experiments was that, when giving an abundance of B, he did not realise that he was giving D as well. It will be necessary in such experiments to turn to account the recognition of the differences between B and D, and thus to plan a diet which shall contain a sufficiency of B without any notable admixture of D. It is not, however, necessary to trouble very much about the supply of B, since experience shows that *adult* experimental animals deprived of B can remain healthy for a period far longer than that which proves fatal from atrophy when D is lacking.

Attention has several times been drawn to the fact that both in experimental polyneuritis and in beriberi the atrophy is not confined to muscle and nerve ; it affects the glands markedly as well, leading to a suppression of the secretions. It is very significant that the pure neuritis without atrophic

manifestations experimentally induced by Simonnet and Karr in their respective series of experiments, was not accompanied by any such signs of glandular atrophy or suppression of secretion. Karr expressly reports that in his experimental animals digestion ran a normal course. This is a plain indication that the absence of D (which is usually found in association with the complettin B) is really responsible for the atrophic manifestations. Even had Simonnet's and Karr's researches been of no other use, we should have to thank them for the clear demonstration they have given that beriberi and experimental polyneuritis are not simple but complex disorders.

When Funk's vitamin is alone lacking, paralyses without atrophy ensue; when D is alone lacking, the result is marasmus with characteristic degenerative manifestations; when both are lacking, the result is typical beriberi or polyneuritis, in which the varying quantities of the respective complettins account for the more or less marked development of one or other syndrome.

Now that these relationships have been cleared up, we are faced with a new and important problem. What is the mode of action of the complettin D? Since the symptoms can appear on a diet which is in other respects adequate, this atrophy can hardly be due to a lack of tissue-building constituents. Besides, there is a fundamental difference between the atrophy we are now considering and that which ensues in a familiar form when some well-known constituent is absent from the diet, or in simple starvation. In D deficiency, we have something more than atrophy due to lack of protein or energy, for there is simultaneous degeneration. Even though we assume that in consequence of the want of D the utilisation of new material and therewith the maintenance of the existing tissues are impaired, this hypothesis by no means suffices to explain the symptoms of degeneration. As previously said, we have no difficulty in conceiving of atrophy without degeneration. But since the two appear in conjunction, there must be some sort of connexion between them; and inasmuch as atrophy does not per se induce degeneration, we are led to infer an inverse order of causation, and to suppose that the atrophy is the outcome of the degeneration. The organism has lost the faculty of maintaining its extant substance, and has therewith lost the faculty of making good the used-up material.

Life, movement, secretion—in a word, all the manifestations of life—are dependent on the using up of the materials of the body. We must not imagine that in this process every cell, or every group of cells, throws off part of its molecular structure, as the dried coats peel off a sprouting onion. We must rather assume that reactions occur within the mass so that the fundamental substance is modified. Nor must we suppose that these changes occur with equal intensity everywhere. According to the nature of the particular vital manifestation, the organ or organs chiefly concerned will be variously modified in their innermost structure. Now the essential feature of life is that whereas the spontaneous decompositions of the inorganic world are irreparable, those that occur in living matter are more or less completely compensated. In malnutrition, and even in actual starvation, the wastage of the organs primarily essential to life is repaired by the withdrawal, from less important organs, of the materials required by the more important ones. If in the case we are now considering, no such repair takes place, if the innermost structural elements do not merely atrophy, but also degenerate, we have to infer that—in contradistinction with the state of affairs in malnutrition or simple starvation—there is a definite lack of something whose presence would render possible the immediate restitution of the utilised material.

We are led by these considerations to discern that the fundamental activity of the complettin D must be a contribution to the restoration of the used-up material. One way of settling the whole question would be to describe the complettin D as a restitutive hormone, as the substance which makes repair possible. But, apart from the fact that we are merely providing a new name instead of giving an explanation, we should have to account for the remarkable fact, unparalleled in the vital processes of the organism, that a hormone indispensable to the individual is, by this supposition, not manufactured by that individual but has to be introduced from without. For just as little as vitamin, can D be synthetised in the animal body.[1036] The best proof of this is that the milk of mothers suffering from latent beriberi is so lacking in these substances that the infants fall ill sooner than the mothers. (On the other hand, such a synthesis is within the competence, not only of the higher plants, but also of the schizomycetes and

the yeasts For instance, the intestinal microorganisms can effect such a synthesis. Consequently, as Portier and Randoin [1063] have shown, the faeces of animals suffering from polyneuritis contains so large a quantity of vitamin that it will suffice to cure the animal if suitably administered.)

More detailed knowledge of these processes is very difficult to acquire, for we are concerned with the most intimate reactions of life, which have hitherto been completely ignored. In the matter of nutrition and repair, modern physiologists, and above all Jacques Loeb, have done a great deal of work, but their labours have by no means sufficed to clear up the difficulties. The main reason for their failure is that the members of this physiological school are completely under the spell of a physical chemistry. Their studies are therefore restricted to two special fields; the effect of the ions on the cells; and the reaction of the living colloidal substance of the cell upon other colloids. Obviously such researches will not unlock all the secrets of the matter, as has indeed been proved once more by Carrel's attempts to induce animal tissues to grow outside the body. For Carrel found that such growth would only take place in natural serum, in the natural fluids of the body.

Moreover, the process of assimilation whereby the cell builds up the constituents of the food into its own substance, and the utilisation of this substance for the purposes of life, can be explained neither in the terms of ionic reactions nor in the terms of colloidal chemistry. Both these fields of research have contributed much towards the elucidation of the bodily processes, but only a purely chemical science can make such processes comprehensible. Here we find ourselves in unexplored country, lacking the guidance of even one established fact.

The explanation of the matters we are considering encounters additional difficulties owing to the entire inadequacy of our anatomical and physiological knowledge for this purpose. It appears to be a fact that to some extent the breaking up, removal, and rendering innocuous of the products of vital reactions is effected by the blood through oxidation, but this statement sums up all that we know of the matter. It is uncertain whether the nutrition of the tissues is achieved by the blood or by the lymph. (I think there are grounds

for giving the preference to the lymph, although the participation of the blood can by no means be excluded.) Our knowledge of this process is all the more inadequate inasmuch as the ultimate course of the finest blood capillaries and lymph capillaries is still unknown to us. Our ignorance makes it very difficult to study these reactions, and physiological science has not yet ventured to approach this fundamental problem.

For example, we do not know where the transformation of the albuminous tissue builders into the body's own substance takes place, and the probability is that there are no special organs for this function. It is unquestionable that not merely every species of animals, but also within each animal every organ, has its own peculiar kind of protein; and it seems unlikely that primarily there should come into existence some sort of standard protein which the individual cells can then metamorphose into their own protein. This would be doing the work twice over, and would render the digestive process superfluous. Far more likely is it that the cells themselves build up their own varieties of protein out of the tissue-building constituents of the food, and the theory that that is how the process takes place has been reinforced by Carrel's success in growing the living tissues. But here we encounter a new contradiction, for this growth was effected in serums which contained, at most, traces of amino-acids in addition to serum albumin. We must not therefore reject the supposition that the cells of the organs have at least some power of transforming an extraneous protein into their own protein. The rapid disappearance of the amino-acids from the fluids of the body after meals is contributory evidence in favour of this view.

If we are in search of explanations of the inner mechanism of the action of the water-soluble antineuritic D, the foregoing theory will seem quite inadequate. There are three facts to bear in mind: the cause of the atrophy or degeneration is, the lack of a certain substance; this substance is not synthetisable in the animal organism, and it is rendered inactive by heating, especially under pressure in a moist medium; finally, the locality where the substance takes effect must be in the cells.

Starting from the last consideration, we can think of

three ways in which the absence of a substance might hinder the rebuilding of tissue. First we might assume that the proper mode of action of the substance in the cell is to promote the synthesis of the cell-substance itself. Secondly we might assume that when the cell is intact and the food is otherwise adequate, the function of the missing substance is to promote the linking of the nutrients to the cell-substance. The third possibility is that through the absence of the substance under consideration, the mixture of nutrients has somehow been rendered inadequate.

To begin with, let us consider the first of these assumptions. The synthesis of the cell-substance proper is achieved in the animal organism with very modest adjuvants—so modest that the process might seem hardly possible. During synthesis in the plant cell, hydration plays a leading part, the addition of molecules of water, or the elimination of groups of atoms by the action of hydrogen. In the organism of higher animals, not a single instance of the kind has been proved to occur. (There are cases of so-called reduction, as when aldehydes are transformed into alcohols with unsatisfied affinities. But these reactions depend upon the addition of water to a compound and its subsequent detachment; they do not depend upon the action of hydrogen.) Nor is there known in the organism of higher animals any instance of the synthesis of carbon chains. Animals obviously lack the power of linking a carbon atom to a carbon atom, of effecting what chemists term a pure condensation. The only condensations the animal organism can achieve are those which take the form of couplings in which carbon is linked to nitrogen or oxygen with the splitting off of ammonia or water, or sometimes with the splitting off of salts—the process whereby ethers, esters, or peptids are formed. On the other hand, the organism is also competent to break up existing compounds by the introduction of a water group or an ammonia group of elements. By these simple reactions, by the alternating addition or subtration of water or ammonia, the most complex proteins can be built up by the animal organism, provided that the necessary carbon chains and amines are supplied in the food.

In the light of the first hypothesis, therefore, we suppose the mode of action of D in the animal cell to be such that

this substance, behaving as an enzyme, either promotes combination or else hydrolytic or aminolytic decomposition. We may, of course, suppose that there is an indirect action like that of a co-enzyme ; but inasmuch as the basic conception is still purely hypothetical, this supposition would involve a superfluous complication. Apart from that, there are good grounds for questioning the accuracy of the whole assumption. First of all, it is hardly conceivable that the animal cell (which fundamentally resembles the plant cell and has come to differ from the latter only through adaptation to a different environment) should be so dependent upon this environment and upon all the alien factors outside the organism as to be incompetent for the spontaneous fulfilment of the very functions by which as a living being it is distinguished from the inorganic world—so that it is compelled to secure the absolutely indispensable enzyme from external sources. An additional reason against any such assumption is that when the food supply is completely cut off, the function we are considering can still be carried out, so that in the organs of the most vital necessity the processes of assimilation continue even though the organism as a whole is foredoomed to death from a lack of the intake of energy. Doubtless the last consideration has no demonstrative force, seeing that death from starvation is a comparatively rapid affair, whereas in polyneuritic disorders the lack of certain substances has to take effect for a long time before the illness begins. There is, however, a third reason for rejecting the enzyme theory as very improbable, for all the organic enzymes hitherto known are comparatively thermolabile. The complettin D, in a dry medium, can resist an hour's heating at 120° C, an exposure which destroys all known organic enzymes.

The second possibility is that there is lacking some sort of intermediate link which, if present, would couple the substances derived from the food to the cell-substance proper. If the suggestion is that we have to do here with something like the amboceptors of serology, it may be incontinently rejected. For in that case we should have to assume that the different substances in the cell all constitute a chemical aggregate which is as it were eaten away at one end by the vital reactions, its integrity being then restored by the linking on of substances derived from the food. But the supposition

is certainly tenable if we presume that some intermediary group may be missing from the food, a group which if present would have enabled the substances in the food to be built up into an aggregate identical with that of the cell-substance itself. If that is the way the second supposition is to be interpreted, we can pass on immediately to the third theory, according to which the missing link is itself a constituent of the food.

The vitally essential requirements of the food would appear to be as follows. It must contain a sufficiency of carbon chains of definite but varying lengths. In part these must be aminised, and in part must contain certain rings. Further, these substances must be sufficiently far reduced. Finally, there must be an adequate supply of groups with unsatisfied affinities, so that the necessary couplings may be possible. The first four requisites are deducible from the proved facts that the organism of higher animals is incompetent to synthetise carbon chains or to effect ring closure (except in so far as this is possible by the simple formation of lactone); that only in the rarest cases can it achieve aminisation; and that it is quite incompetent to effect hydration. The fifth requisite is obvious, seeing that the new substance required by the organism has to be built up by couplings.

To decide where in this instance the defect may lie, we must further make allowance for the fact that although the substance in question is generally believed to be fairly thermostable it is certainly damaged by prolonged heating. Under the conditions that obtain we may exclude the possibility of a decomposition of a carbon compound by over-heating, or the decomposition of the possible ring-closing substances. It is, however, perfectly conceivable that sensitive amines can be saponified by heat, especially in the presence of water, the amine group being replaced by a hydroxyl group; and Abderhalden's researches have shown that the hydroxides cannot replace the amines of the food—cannot be re-aminised. This possibility must, therefore, be borne in mind; but the theory is rather improbable, seeing that the amines hitherto known to be present in the food and in our organism are not very sensitive to heat. Among the synthetic amines, there are certainly many in which, owing to peculiar structural conditions, the amine group is readily detachable, but no

such substances are known among the natural amines. Still, the possibility must not be absolutely dismissed, for it is known that the water in which meat has been boiled contains more ammonia than was demonstrable in the meat. The question arises, however, whether this splitting off is not comparable to that which occurs as a purely physiological accompaniment of digestion without any bearing on nutrition, as when carbamides are transformed into the corresponding ammonium compounds.

There is a second group of comparatively unstable substances in natural foods, comprising what is known as the sulphhydril group. Hirschstein [259] has drawn attention to these. In the hydrolysis of proteins in the laboratory we find as the primary representative of the sulphur compounds cystin, which is an anhydride of the sulphhydrate cystein. In our discussion of the biological value of the proteins we learned that these substances are absolutely essential to life. Cystin is a very unstable substance. We are entitled to ask whether cystein, too, may not be of great importance for the upbuilding of proteins, seeing that it is even more unstable than the anhydride. A possible objection to such a view is that a sulphur-free diet is rendered adequate by the addition of cystin ; but there is no reason why we should not assume that in the body this anhydride may take up water and undergo decomposition into oxy-amino-propionic acid and cystein, so that the really active body is the sulphhydrate. At any rate, we know that in the food, cystin can be replaced by cystein ; and it is certain that when either of these substances is heated in the presence of water, the sulphur is split off. Thereby, both cystin and cystein are obviously rendered valueless for nutritive purposes, inasmuch as sulphhydration cannot be effected in the animal body. The fact that this decomposition is not merely possible in the circumstances we are considering, but does actually occur, is proved by the fact that when tins of preserved meat are opened a fairly definite odour of sulphuretted hydrogen is often perceptible. During the war, the sterilisation of tinned meat was so ruthlessly conducted that complaints of this smell became quite common.

Besides the sulphur group, we have reason to suppose that the food contains other groups of substances with a

readily modifiable composition (for instance, bodies with an aldehyde-like structure), but our knowledge of these is too vague to justify definite statements concerning them. We are, however, certain that the proteins, and especially the nucleoproteins, contain thermolabile mixed-organic compounds. Thus it is supposed that part, at least, of the phosphoric acid in the nucleoproteins must be present in the form of metaphosphoric-acid compounds; and on prolonged boiling in water these, even when combined with bases to form metaphosphates, are more or less rapidly transformed into orthophosphates. This may be taken as a partial confirmation of Schaumann's views concerning the indispensability of certain organic phosphorus compounds, for the animal organism is unquestionably competent to change the lower stages of oxidation of phosphorus, such as metaphosphates and pyrophosphates, into orthophosphates, but cannot effect a reversal of the process.

Simple prolonged heating of foodstuffs, especially at a high temperature or under pressure, may therefore be presumed capable of bringing about any one of three changes competent to render inadequate an otherwise adequate nutrient, because the animal organism cannot reverse the transformation. These are: (1) the disaminisation of vitally important amine compounds; (2) the decomposition of similar sulphur compounds (and perhaps of substances belonging to other unstable groups); (3) the metamorphosis of metaphosphates and pyrophosphates into orthophosphates. Reactions (1) and (2) will make it impossible for the foodstuffs to be assimilated to form cell-substance, for the unstable groups in the food mixture will have been destroyed. In the case of reaction (3) the unfavourable effect is twofold: in the first place the food will have been deprived of the metaphosphoric and pyrophosphoric radicals, which are essential to nutrition; and secondly the aid to the process of coupling which would have been furnished by these phosphorus derivatives, will now be lacking.

In the second chapter we learned that the lower-grade amino-acids are apparently of no vital importance, seeing that they can be formed within the body out of higher compounds by simple oxidation. When, therefore, we think of disaminisation as a pathogenic influence, it is only the amino-acids of

high molecular weight that come into the question, but these are present solely in comparatively small quantities in prophylactic or curative D-containing extracts. But there is evidence telling against the theory that disaminisation by heating is of much importance in this connexion. For instance, in the sufferers from beriberi in Mesopotamia, the meat rations had been lavish. If, therefore, we are to regard the lack of certain amino-acids as the essential cause of the malnutrition, we must suppose that the meat must have been quite disintegrated by the process of sterilisation—a far more thorough disintegration than can be effected in the chemical laboratory during artificial hydrolysis. I therefore consider that the disaminisation factor may be dismissed from the reckoning.

Again, complete disintegration of the sulphur compounds is hardly conceivable even in ultra-sterilised meat, so that this assumption has little probability in its favour.

With regard to the third hypothesis, on the other hand, the experiments of Francis and Trowbridge [114] and those of Trowbridge and Stanley [115] have shown that when meat is boiled even for a comparatively brief period, organic phosphates are transformed into inorganic. I consider that in connexion with the appearance of beriberi in persons on a sterilised diet, this is the factor we have chiefly to consider accountable for the causation of the atrophy and degeneration of muscles, nerves, and glandular tissues. Thus we come back to the early view of Schaumann, that the lack of organic phosphorus compounds must play a leading part in the etiology of polyneuritic disorders. If dosage with "organic phosphates" failed to do any good, this was because the phosphates given were not those vitally essential phosphates normally present in the food. The phosphorus compounds used in the experiments have for the most part been mixed-organic compounds, simple ester-like combinations of ordinary orthophosphoric acid, not containing the metaphosphates and pyrophosphates that are indispensable to the animal organism.

This must not be interpreted as an assertion that metaphosphates or pyrophosphates would be effective as such, for it is quite possible that what counts is their mode of combination in organic matter. No doubt when we hydrolyse organic substances containing phosphorus, we find these phosphates; but it does not follow that the animal organism

is competent to produce them. We know, indeed, that when digestive enzyme acts on the nucleoproteins, phosphoric acid is split off provided the action is continued long enough; however, the latest investigations point to the conclusion that in natural digestion no such complete splitting off takes place, but that larger and more complex compounds are absorbed from the alimentary canal.

Until further study has supplied us with better lights, we are entitled to accept as a working hypothesis that in these illnesses the repair of tissue waste has been rendered impossible by the lack of certain organic phosphorus compounds in the food. This lack is in some cases due to the direct removal of certain ingredients, as in the "polishing" of rice, or in the boiling of food and the subsequent throwing away of the water used for the purpose; and in some cases it is due to the destruction of thermolabile substances by excessive or unduly prolonged heating. Hence the atrophic changes in the affected organs, for continued work without the replacement of the used-up material must in the long run infallibly cause degeneration. An additional factor is undoubtedly the lack of catalase, owing to which the catabolic changes must run an abnormal course. A further source of trouble is that the medium in which tissue change has to be effected is rendered unfavourable, on the one hand by the presence of these products of abnormal catabolism, and on the other hand by a deficiency of inorganic constituents.

An objection which may be put forward against the foregoing theory is that in starvation states, when the supply of the same substances is likewise absent, though atrophy ensues, there is no degeneration. We must, however, remember that in starvation the course is far more rapid, and that in polyneuritic disorders the period of incubation is often considerably longer than is requisite in starvation for a fatal result. It has, moreover, been proved that during starvation the most vital organs are nourished at the expense of the others, in order that the former may be kept supplied with adequate nutriment. In starvation, therefore, the less important organs atrophy, and will at most exhibit degenerative phenomena towards the very last, whereas during the prolonged incubation of polyneuritis there is plenty of time for degeneration to ensue

CHAPTER FIVE

THE CONDITIONS OF GROWTH

1. Introductory.

The old schematisation of the theory of nutrition, with its undue stressing of the importance of the supply of protein and energy, wrought much harm, and nowhere was the harm so manifest as in the domain of the feeding of children. Suffice it to recall how authorities in dietetics, ignoring the increased demand for food dependent upon growth, were content to estimate children's need for nutriment as proportional to size and weight. So hidebound was the application of this principle that we are really entitled to wonder that the nutritive requirements of infants-in-arms during the first weeks of life were not supposed to be restricted to 2 % of the requirements of the adult. A good many years ago I pointed out that growth necessarily demands a far more active turnover, and that for this reason the nutritive requirements during growth must be incomparably greater than those of adults. I showed further that, thanks to the pedantry which ignored this consideration, the results of all the investigations regarding the nutrition of the population of the United States (investigations which have cost many millions of dollars) have been worthless. During the last decade there has been a change for the better, though at first, it would seem, only on the other side of the Atlantic. Thus in 1920 M. A. Brown [1008] declared that the nutritive requirements of the growing organism had hitherto been greatly underestimated. Despite theory, in practice, when children are not thriving, those responsible for their care are always ready to try and enforce improvement by an extravagant supply of nutriment, chiefly in the form of protein,

but sometimes in that of carbohydrate or fat. Witness the innumerable proprietary preparations for the feeding of children with which the market has been flooded for decades. The very multiplicity of these preparations is the best proof that most of them are ineffective, and that those who recommend and use them are on the wrong road. The trouble is that, as Terrien [1218] phrases it, far too much faith has been put in the so-called dietetic test. The mere fact that by an excessive supply of nutriment it is possible to cause an increase in weight, by no means signifies that the development of the growing organism has necessarily been redirected into the right channels. To justify a conviction that such an improvement has occurred, we must ascertain by detailed and accurate observation that absorption and excretion are properly related each to the other, and that the increase in weight is not due to a morbid deposit of fat or a morbid retention of water in the tissues.

Here prolonged observation is requisite, and the medical practitioner is seldom able to undertake anything of the kind. The patient is brought to see the doctor once or twice at the ordinary hours of consultation, and that is all. There may or may not be improvement. Unless improvement is immediate and obvious, the parents are apt to grow impatient and to consult another physician, who will have a different method. While each adviser, guided simply by the increase in weight, may be convinced that his prescriptions have been helpful, in the unfortunate little patient grave disorders of health are gradually developing, and the specialist whose advice is ultimately sought may be unable to ascertain their direct cause.

The disastrous results of the present methods of child feeding in our large towns should suffice to convince anyone that the period of observation should be much longer than is now customary. If we are to draw sound conclusions as to the value of any particular diet, it is not enough that we should be able to show that one individual apparently thrives upon it. Osborne [1224] is right in maintaining that in many cases the effects of errors of nutrition do not become noticeable for three or four generations, and the assertion has been endorsed by numerous other investigators. *How many*

instances of so-called degeneration, of anatomical hindrances to childbirth, of incapacity for procreation, conception, lactation, etc., are referable to dietetic errors in earlier generations!

It is obvious that the life of the individual human being is too short to enable any one of us to make a sufficiency of observations in the case of the human young. On the other hand, we must carefully avoid a premature application to human conditions of the results of experiments on animals. But when it is possible to trace a close parallelism in these respects between human beings and the lower animals, the transference of conclusions is justified. Above all, it is justified when the same causes produce the same effects in the most diverse classes of animals, as in birds, rodents, ruminants, omnivora, and carnivora, and when it is possible to prove that in a comparatively short time these causes produce the same effects in human beings. Then we may apply to human dietetics what we have learned from experiments on animals. We saw in the last chapter how valuable this method has been in the case of the polyneuritic disorders, notwithstanding the fact that we may be disinclined to regard the experimental polyneuritis of birds as perfectly identical with beriberi in human beings. From this outlook, the investigations of the last decade, and especially those of very recent years, although they have been carried out on animals, are of overwhelming importance in their application to dietetics in the case of adult human beings no less than in that of children

2. Importance of Protein.

In the second chapter a detailed account of the importance of protein was given. Most of the experiments upon which that account was based were made and confirmed upon growing organisms, and as far as generalities are concerned it will suffice to refer to what has previously been said. All that I need add here is that, thanks to the dominant tendency to overestimate the importance of protein, substances shown by a cursory chemical examination to contain a considerable percentage of crude protein are often esteemed far more highly than their merits warrant. Let me recall the wartime attempts in Germany to supply a richly albuminous nutrient derived from yeast. To make "nutritive yeast" (as it was

pompously styled) money was spent by the million, large quantities of sugar being wasted in the process—though sugar was exceedingly scarce and was urgently required for the feeding of the people. This sugar was literally thrown away, for physiological experiments on nutrition have proved that the crude protein which "nutritive yeast" certainly does contain in very large quantities, partly consists of free amino-acids and is partly of low biological value, so that ordinary potato protein is a far better nutrient. (Cf. Funk, Lyle, and McCaskey.[567]) In brief experiments on human beings, Wintz [530] did, indeed, find that *when the rest of the protein in the diet was high-grade*, as much as 30 to 40 % of the protein could be given in the form of yeast protein and effectively utilised; but the exhaustive researches of Hawk, Smith, and Holder [871] have shown that in ordinary circumstances the amount of "nutritive yeast" protein in the diet cannot usefully exceed from 10 to 30 %. Moreover, the use of yeast protein is restricted by the fact that not more than one or two grammes can be tolerated. When as much as four grammes are given, diarrhoea sets in.

In like manner the crude protein of the pulses that ordinarily ripen in Germany is far too highly esteemed. In my own experiments,[319, 614, 785] the protein requirement of an adult human being could not be tolerably well supplied by a smaller quantity than ten pounds of haricot beans daily. McCollum, Simmonds, and Pitz,[645] and McCollum, Simmonds, and Parsons,[691] report that the protein of ripe peas, beans, and lupines is quite inadequate to maintain growth.

It is essential to remember that many varieties of protein that are able in an emergency to keep an adult going (the whole rye grain, for instance [896]), are incompetent to provide for normal reproduction, or to ensure a proper secretion of milk. Consequently, when the diet is ill-balanced, and when these sorts of protein predominate, the offspring may suffer seriously even though the parents may seem to be doing well on such a diet.

The following varieties of protein are known to be quite inadequate to maintain growth: the aggregate protein from beans, peas, and lupines [645, 691, 896]; phaseolin,[225, 423] legumin, and vignin (which are able at most to keep up the body-

weight [225, 423]; rye,[896] wheat,[515, 579, 598, 801, 896] barley,[740, 896] oats,[598, 625, 896] rice,[896] maize,[896] soy beans,[896] zein,[225, 423] conglutin,[225, 423] hordein (can only maintain weight [225, 423]), gliadin (can only maintain weight [225, 246, 423, 550]), carrots,[784] gelatin,[225, 423] bananas.[775, 968]

It is true that in certain parts of the before-mentioned nutrients we find varieties of protein which are able to function as efficient growth-factors, such as edestin (badly ! [541]) excelsin,[225, 423] maize glutelin,[225, 423] and the protein of the wheat germ.[507] But these adequate proteins are not present in quantities sufficient to supply the needs of the growing organism. Since, however, the various proteins differ greatly in composition, it is sometimes possible to induce satisfactory growth by a mixture of foodstuffs each of which is separately inadequate. It is important that the ingredients of such a mixture should not belong to the same class of foodstuffs, for within any one class the proteins will usually be found to have the same general composition, and therefore to present identical defects. The leading defect, as a rule, is an insufficiency of certain ring compounds—such amino-acids as tryptophan or tryosin, and above all an insufficiency of lysin and cystin. Hence the cereals, which are poorly furnished with lysin, are per se quite inadequate, but can be rendered adequate as growth-factors by the addition of gelatin, since this substance contains 6 % of lysin.[598, 625]

There is not a very large choice of really adequate nutrients. Among seeds, the only ones we know to be adequate are cotton seeds, for cottonseed meal, when not too finely sifted, suffices to maintain growth.[4939, 524, 550, 654] Furthermore, cottonseed globulin is adequate, as is also pumpkinseed globulin.[225, 423] Potato protein,[567] too, is adequate ; my own experiments showed this protein to have an unexpectedly high biological value. Eggs,[319, 749] and also the separate proteins they contain (ovalbumin and vitellin), are adequate growth-factors.[225, 423] In my own experiments, the adequate protein of milk was found to resemble the adequate protein of egg in possessing the very highest biological value.[785] As regards lactalbumin, its high biological value has also been proved by experiments on animals,[225, 423, 541] although Chick and Dalyell have shown [1278] that by supple-

menting lactalbumin with small quantities of cystin a further increment of growth can be secured. Opinions differ as regards casein. In experiments of only 30 days' duration, Osborne and Mendel [225, 423] found that casein could maintain normal growth in mice; but subsequently they reported that it was only two-thirds as effective as lactalbumin [541]; by the addition of small quantities of cystin, casein could be rendered as good a growth-factor as lactalbumin. This may explain Hopkins' observation,[202] that casein was not fully adequate, but could be rendered adequate by supplementing it with very small quantities of milk—quantities so small as to increase the amount of dry substance in the food by only 4 %. Still, we must not reject the possibility that in Hopkins' experiments the mixture of salts employed may not have been fully adequate, and that the beneficial effect of the addition of milk may have been due to the salts in the milk rather than to the small quantities of lactalbumin it contained. Finally, Osborne and Mendel have drawn attention to the fact that what is called " protein-free milk " really contains small quantities of cystin. This may account both for the improvement in the efficiency of casein noted in Hopkins' experiments when milk was added, and for the great superiority of natural milk to isolated lactalbumin or casein.

I must not omit to mention the opinion of many investigators that, after a certain age, milk is unsuitable as the sole source of protein. Freise [1006] agrees with Mattill and Conklin [1285] in referring this unsuitability to the fact that milk is not a sufficiently concentrated food, and they have secured far better results when fresh milk has been to a large extent replaced by dried milk. But these same experiments really show that the reputed inadequacy is not due to any defect in the composition of milk protein, but obviously to the modified requirements of the adult organism in the matter of inorganic constituents.

It has been shown in the foregoing that inadequate proteins can sometimes be rendered adequate by supplementing them with other proteins which are likewise inadequate when used exclusively. Obviously, then, an inadequate protein can be still more easily supplemented by an adequate protein. For instance, maize may be converted into an adequate growth-

factor by adding blood [346, 568] or milk [1143]; maize gluten, by lactalbumin or cottonseed meal [550]; cereals, by gluten, casein, yolk of egg, or milk [409]; maize by lactalbumin [613]; rice, [454] or seed protein in general, [579] or bananas, [775] or carrots, [784] etc., by casein. The amount of the supplementary protein required is comparatively small, and Osborne and Mendel [613] draw special attention to the fact that it is far less than would be needed if the supplementary protein had to function as the sole source of protein.

In the second chapter we learned that the minimal quantities of protein needed to maintain weight have hitherto, as a rule, been overestimated. The statement is less applicable to the period that immediately follows birth, for at that time, owing to the demands of growth, comparatively large quantities of protein are required. Still, the difference between the minimal amount needed to maintain weight and the optimal requirement for growth is not very large. McCollum and Davis [425] report that in the case of young rats for the maintenance of weight the minimum proportion of milk protein needed in the food is 3 %; that, as the proportion of milk protein is increased, growth proceeds more rapidly until the amount of milk protein in the food reaches 8 %; this is the optimum, for further increments of protein do not advantage growth in any way. Several years earlier, Osborne and Mendel [225] had come to the same conclusion.

If the quantity of protein is kept near the minimum, or at any rate well below the optimum, an increase in fats or in carbohydrates, even though considerable, does not exercise a favourable influence on growth. [851] This observation conflicts with the generally received opinion, but it accords perfectly with the demands of the law of the minimum. When the amount of protein in the diet is reduced, the experiments of Richardson and Green [654] show that the first effect is that the rate of growth falls off, and that when the protein is reduced to the minimum that will maintain weight, growth is completely arrested. If, now, the amount of protein in the diet is yet further reduced, loss of weight ensues.

Of course the level of both the minimum and the optimum is mainly determined by the nature of the protein used as food. In addition, however, the relationship between the

protein and the total supply of energy plays a notable part.[837] Though, as already said, assuming that a definite amount of protein is being given, even an immoderate increase in the supply of energy in the food fails to exert any influence on growth, Bierry [833] is right in insisting that a minimal supply of protein carries with it the need for a minimal supply both of fat and of carbohydrate.

3. Importance of inorganic Substances.

Nevertheless, a diet containing adequate amounts of protein, fat, and carbohydrate, is still far from being competent even to maintain the body-weight, let alone maintain normal growth. In Chapter Three the importance of the inorganic constituents of the food has already been discussed. Here I need merely point out that it is not enough for the food simply to contain inorganic salts; what is indispensable to an adequate diet is that the supply of inorganic constituents, and the varying quantities of the respective salts, should be duly related to the age of the individual under consideration, to his bodily and mental condition, to the nature of the nutriment he has hitherto been receiving, and to the present supply of food. We have learned with regard to the inorganic ingredients, that not merely must there be a sufficient minimum of each, but that they are mutually interdependent, so that the various minima are not constants (as has hitherto been generally assumed by dietetic experts). The supply of the inorganic constituents of the diet must therefore be adapted to the supply of the respective organic constituents; and above all to that of the protein in the diet, for protein contains an excess of sulphur and phosphorus, which in the healthy organism are oxidised to form the corresponding acids, requiring for their excretion a suitable supply of bases in the food. The conditions that regulate the bodily requirements in respect of protein are already complicated enough; but it follows that the conditions that regulate the bodily requirements in respect of inorganic constituents must be no less intricate.

It must be remembered, too, that, in the growing organism, metabolism is necessarily far more active than in the adult organism, and that the increased turnover in the former creates a far greater demand for inorganic nutrients. There

are two substances in particular of which the adult organism has comparatively little need, whereas in the growing organism the demand for them is exceedingly active. I refer to iron and calcium. As far as sucklings are concerned, nature attends liberally to the matter: for at the beginning of its earthly pilgrimage the immature being receives an ample provision of iron from the maternal store; and milk is extraordinarily rich in calcium salts. But when the sources of milk run dry, the prospects of an adequate supply of calcium are greatly restricted.

It is a good thing, therefore, that, by the very fact of growth, the growing organism is enabled to utilise the calcium salts of the food in a way impossible to adults. The adult has to devote a large proportion of the calcium supplied in the food (and what is said here of calcium, applies on the whole to magnesium as well) to promoting the excretion of the excess of phosphoric acid contained in the diet. In the suckling, on the other hand, there is an active demand for purely inorganic phosphoric acid no less than for calcium, seeing that the former is needed as well as the latter for the building up of the osseous system. In the adult organism, large quantities of tricalcium phosphate are excreted as excess of ballast by the mucous membrane of the large intestine, and are eliminated with the faeces; but in the growing organism they are built up into the substance of the bones. Here is a characteristic difference between the metabolisms of the respective ages.

In the third chapter we learned that, in respect of inorganic ingredients, foodstuffs can be divided into two main groups, respectively containing an excess of bases and an excess of acids. Apart from the artificialities introduced by civilisation and by its dealings with the cultivated plants, the distinction is a sharp one and is of fundamental importance. Furthermore, we saw that within each of these main groups the different classes of foodstuffs have their own peculiarities. For example, the proteins of most seeds, and especially those of the cereals, are especially characterised by inadequacy due to a lack of cystin and lysin. In like manner, it is a common characteristic of seeds, not only to contain an excess of acid, but also to exhibit a deficiency of calcium. For lime is almost always

present in the soil, so that seeds need not contain any more calcium than is requisite to provide for the growth of the first rootlet. In growing animal organisms, on the other hand, the need for calcium is very great. *Cereals, consequently, quite apart from the fact that they contain an excess of acid, are about the most unsuitable food we can force upon the growing animal organism.* The best proof of this is that even graminivorous birds collect insects to nourish their young. The fledglings of the most strictly vegetarian birds are carnivora!

I am merely repeating here what I have said time and again elsewhere, but it will be well for me to show how extensively recent study of the determinants of growth proves that we are concerned with something more solid than ingenious speculations of my own. Enough to refer to especially important and characteristic researches. Funk,[527] McCollum, Simmonds, and Pitz,[625] and Hess and Unger,[750] state that the supply of inorganic salts in oats (whether the whole grain or the meal) is inadequate for the upbringing of young animals. Hart, Halpin, and Steenbock [655] inform us that wheat cannot maintain growth unless supplemented with basic sodium and calcium salts; and according to McCollum, Simmonds, and Pitz,[507] the germ of the wheat grain is likewise inadequate as a growth-factor. The latter make the same report regarding rice; and McCollum and Davis [454] state that rice is deficient in bases. The mineral content of barley is quite insufficient for the needs of the growing animal organism, and this grain must be supplemented by a complete mixture of nutritive salts.[740] Various reports are available as concerns the supplemental need for inorganic salts in animals fed on maize. McCollum, Simmonds, and Pitz,[578] Hogan,[634] Hart, Halpin, and Steenbock,[655] and Osborne, Mendel, and Wakeman,[1280] all lay stress on the deficiency of calcium in maize, saying that there is not even enough to supply the needs of the adult pig; and Hogan [568] further insists that, for the promotion of growth, a maize diet must be supplemented by sodium and chlorine in addition to calcium. McCollum, Simmonds, and Parsons,[691] and Hart and Steenbock,[956] make the general statement that for the maintenance of growth the cereals must be supplemented by sodium, calcium, iodine, and perhaps

chlorine as well ; and Hart, and McCollum [409] expressly declare that all the cereals contain an excess of acid, and that a cereal diet therefore requires the addition of inorganic bases.

Cotton seeds are an exception to the general run of seeds, for they contain a protein that is fairly competent to maintain growth. Richardson and Green [524] found, however, that these seeds likewise are inadequately furnished with calcium and other bases. According to McCollum, Simmonds, and Parsons,[691] haricot beans are not able to maintain growth unless their protein and complettins are supplemented by the addition of calcium carbonate and sodium chloride ; and McCollum, Simmonds, and Pitz [645] state that the pulses generally are inadequately supplied with sodium and calcium. McCollum and Davis [431] report that seeds as a class are lacking in inorganic nutrients, and must be supplemented by mixtures of inorganic salts.

Bananas, again, are too poor in calcium to be adequate growth-factors.[775, 780, 980] Roots and tubers are often greatly deficient in calcium, and sometimes deficient in sodium. According to McCollum, Simmonds, and Parsons,[777] this is especially true of potatoes ; and according to Denton and Kohmann,[784] of carrots.

Various authors emphasise the difference, from the nutritional outlook, between the green parts of plants and the seeds. Whereas the seeds contain an excess of acids, the leaves contain an excess of bases ; and whereas all seeds are deficient in calcium and sodium, leaves are often richly supplied with these bases. McCollum and Davis [431] have shown in their experiments that omnivora (such as pigs and rats) fed on grain can rear their young provided that the grain is adequately supplemented with green fodder. McCollum, Simmonds, and Pitz,[645] even in experiments on birds, supplement grain feeding by giving leaves rich in sodium and potassium ; and they point out that under natural conditions the graminivora do not live exclusively on grain, but have a great liking for young and tender greenstuff—for instance, they nip off and swallow whole the fresh shoots of newly germinated plants. In view of these facts it is rather remarkable to find McCollum (McCollum and Davis [440]) maintaining that the alkalinity or acidity of the food has no influence on

nutrition. This strange assertion is explicable on the ground that for the estimation of the base-acid ratio McCollum employed the obsolete and fallacious method of titration of ash alkalinity. The method will often disclose ash with an alkaline reaction in foods which a more accurate analysis shows to contain a marked excess of acid; during the process of conversion to ash, the greater part of the sulphur and chlorine often disappears. This is why McCollum and his collaborators, in preparing their artificial mixtures of salts, have paid insufficient attention to the supply of bases, so that their mixtures are inadequate in that respect. Owing to the fact that their mixtures do not contain a sufficient excess of alkali, their successes in the upbringing of young animals cannot be compared with those of Osborne and his pupils, who used mixtures of inorganic salts containing a more notable excess of alkalies. Thus a single defect in analytical technique can introduce the greatest confusion into the results!

4. Importance of the Methods of Preparing Food.

It is necessary to insist once more that nutrients may not only be primarily inadequate in respect of their content of inorganic salts; they may be primarily adequate, but may be rendered inadequate by the method of preparing the food. For example, the cereals already have a poor equipment of inorganic salts; if now, in preparing pap for children, only the finest sorts of meal be employed, we are using a substance from which the greater part of the salts has been discarded, so that such a food may be directly pathogenic. Again, the common practice of throwing away the water in which food has been boiled, leads in many instances to a dangerous impoverishment in the inorganic constituents of the diet. (Vide supra, pp. 73, 125, and 171.) Furthermore, measures that might be supposed to have no effect of this kind, such as the sterilisation of milk, may in certain circumstances bring about important changes in the mineral content of a foodstuff. We have already learned that when milk is sterilised by heat, the calcium-magnesium-carbonophosphate it contains (a salt indispensable to the upbuilding of the bones) breaks up into its constituent salts,

and that three of these, namely calcium phosphate, magnesium phosphate, and calcium carbonate, are quite insoluble. Not merely does there result an impairment of the physiological working of the substances in question; but further, as McCollum and Parsons [1300] have shown, a partial coagulation of the milk protein ensues during the sterilisation. The coagulated portion is precipitated with the salts, and clings firmly to the wall of the container. Thus the simple sterilisation of milk, as for example in a Soxhlet apparatus, leads to a physiologically important reduction in the bone-forming salts of the milk.

The author is, therefore, in full accord with Osborne,[1224] who insists, that *the urgent interest and novelty of the complettin problem must not lead us to forget the decisive importance of the inorganic salts.*

5. The fat-soluble Complettin A.

It has been proved that normal growth cannot be secured by the most sedulous attention to the four great classes of footstuffs hitherto recognised. An adequate supply of proteins, fats, carbohydrates, and inorganic salts, is far from sufficing in this respect. The priority here must certainly be given to G. Lunin,[3] who showed as long ago as 1881 that substances of a hitherto unknown character, essential to growth, were apparently present in milk. The statement was confirmed in 1912 by F. G. Hopkins.[202] Almost simultaneously, Osborne and Mendel [225] drew attention to the same fact, and investigators generally now became aware that water-soluble growth-factors must be important ingredients of food. As early as 1909, W. Stepp [93] recorded the pioneer observation that nutrients which have been extracted with alcohol and ether cannot maintain life in mice; but that if the alcoholic extract has been made in the cold, its readdition to the nutrients renders them adequate once more. In this connection, physiologists were at first inclined to think of the lipoids, some of which are soluble in alcohol.

In the following year, however, Osborne and Mendel [305] showed that the factor under consideration was not universally present in fats. For instance, normal growth does not take place in animals fed on an artificial diet in which the sole

fat is lard or dripping; but if a little butter be added to the diet, or if butter be substituted for the lard or dripping, normal growth is resumed. In these experiments it was also proved that the fat-soluble growth-factor must be an ingredient of those portions of the butter fat that have a comparatively low melting-point. When the butter was melted at a moderate temperature and centrifuged, the growth-factor was concentrated in the clear butyric oil. Inasmuch as this butyric oil is practically free from nitrogen and phosphorus, it was manifest that the growth-factor could not belong to the lipoid class.

Much interest was aroused by this discovery, and numerous investigators now attempted to elucidate the nature and mode of action of the complettin A. Since the effects of this substance are not confined to the promotion of growth, it will be necessary to devote a special chapter to the fat-soluble complettin A, and for the nonce we need concern ourselves only with its function as growth-factor.

The researches of McCollum and Davis, [453,454] and those of Drummond, [499] and others, speedily showed that this complettin A is in fact indispensable to growth. The presence of the substance in butter was confirmed by McCollum and Davis, also by Aron,[448] and by Langstein and Edelstein.[730,780] Codliver oil, and fish oil generally, contain it in abundance [896]; so does the body-fat of beeves, whereas the storage fat contains very little.[634] Among the vegetable oils, linseed oil [691] is extremely poor in this constituent; and olive oil and rape-seed oil [730, 780, 896] contain but little. Cocoanut oil, and the palmin or vegetable margarine made from it, are very ill-supplied with the growth-factor [730, 780]; whereas animal margarine manufactured from oleomargarine or olein contains a fair amount, though not nearly so much as real butter. On the other hand, the stearin residues obtained by pressure as a by-product in the manufacture of animal margarine is devoid of the complettin A.[424] Seeds contain very little, and are therefore inadequate foods in this respect; millet, hemp seeds, [636, 682, 691] and cotton seeds,[524, 654] are exceptions. Among the cereals, oatmeal (which has of late been so widely recommended as a food for children!) is particularly poor in A, and is therefore incompetent to pro-

mote growth.[625, 750] Maize,[568] rice,[454, 507] and barley,[740] are not much better; nor is wheat, this statement applying both to the whole grain and to the germ.[507, 515] Whereas the cereals in general contain too little A,[409] some of the pulses are adequately supplied; the soy bean is notably rich in this substance.[645] Bananas have too little [775]; so have potatoes.[777]

The discovery was soon made that the A content of a fat is greater in proportion as the fat is of a richer yellow tint. Then it became apparent that this is likewise true of root crops; whereas potatoes, which are colourless, contain very little A, carrots, and in especial the more richly coloured varieties, contain an ample supply. More careful researches showed, however, that the association of a high lipochrome content with a high A content is merely fortuitous; nutrients containing much lipochrome may sometimes contain little A, and conversely nutrients containing little lipochrome may contain much A. Further investigations disclosed the fact that fat-soluble A may be present in a foodstuff that contains no fat at all, or practically none. Green leaves, for instance, which (except for their minimal supply of leaf-wax) are almost devoid of fat, frequently contain considerable quantities of A—more than most fats contain.

Mellanby [1135] is, indeed, disposed to consider that the importance of A as a growth-factor is inconsiderable, for in his experiments, in which dogs were given a diet containing very little of this complettin, growth seemed to be independent of the A content of the food. He quotes as contributory evidence the experiments of Hess and Unger, in which the growth of children fed on dried skim-milk, sugar, cottonseed oil, autolysed yeast, orange juice, and flour, was perfectly normal—for Mellanby holds that this diet was practically devoid of A. But neither Mellanby's own experiments on dogs, nor those of Hess and Unger on children, are conclusive as to the indispensability of A as growth-factor, seeing that the assumption that the complettin A is met with only in animal fats is absolutely erroneous. Later investigations have shown that skim-milk, and also Osborne's protein-free milk, contain notable quantities of A. Even the casein of commerce manufactured from skim-milk, and the lactose of commerce prepared from whey, often contain A,

sometimes in considerable amount. If we further bear in mind that cottonseed oil, autolysed yeast, cereals, and, in especial, orange juice, all contain a fair proportion of A, we shall readily understand how, in the diets specified by Mellanby, the summation of the small quantities of A in the various nutrients can easily have produced a total fully adequate to maintain normal growth.

Before leaving the complettin A, it will be as well to make perfectly clear that A is not identical with either the lipochromes or the lipoids. The investigations of Palmer and Kempster [959, 960, 961] have shown that the substances belonging to these categories have no effect on growth. In addition, we must note that the complettin A exhibits a notable degree of thermostability. It does not seem to be any the worse for prolonged boiling (in milk), or even for prolonged heating to over 120° C. (in butter). It is, however, very sensitive to the oxygen of the air. Its efficacy is seriously impaired when butter containing it is brought to a temperature of 100° C. and vigorously stirred; while if air is forced through the melted butter, the complettin is rapidly destroyed.

6. The growth-complettin water-soluble B.

a. Historical.

The part played by the complettin A as a growth-factor has not yet been fully elucidated, although it is known that A certainly does function in that capacity. It is much the same with the water-soluble growth-factor, the complettin B. True, that the previously quoted observations of Hopkins and Funk refer mainly to the complettin A; and Funk's original assumption was that a diet containing both A and vitamin was fully adequate for the maintenance of growth. But this acute observer soon realised that in addition to vitamin there must be other water-soluble substances of fundamental importance. More especially he learned from the experiments he published in 1913 and 1914 that adequate growth could not be secured by an artificial diet rich in vitamin unless it also contained the second water-soluble growth-factor.[315, 323, 324, 388] His researches were soon confirmed by other investigators, and McCollum and Davis [453, 454]

expressly declared that a special water-soluble growth factor must be indispensable in addition to Funk's vitamin and the fat-soluble factor A. Drummond,[499] and at an earlier date Osborne and Mendel,[225] found that milk contained water-soluble growth-factor in the absence of which normal growth was impossible; and Drummond secured similar results with the lactose of commerce. We may parenthetically remark that Funk [388] assumed that this growth-factor had in the adult organism to be destroyed by some sort of specific reaction; he held that the formation of malignant tumours must be due to a failure to effect a sufficient destruction of the water-soluble growth-complettin in the adult organism. This complettin, he imagined, becoming concentrated in some part of the body which, for one cause or another, was peculiarly predisposed to such a concentration, gave rise to a crude and uncontrolled proliferation of the tissue cells.

McCollum and Simmonds [661] made interesting and exhaustive researches on growing animals whereby the applicability of the law of the minimum to the growth-complettins was demonstrated. From these experiments it appeared that when the food contained only A or only B, even in marked excess, the animals speedily perished. Either A or B might be given in quantities just sufficient to maintain weight, but this could not keep the animal alive for long. It soon became weak and succumbed to prostration. If A or B were given to satisfy the minimal requirement, and the other complettin were provided in excess, weight could be maintained, but the animal died just as quickly as if both A and B had been reduced to the minimum requisite to maintain weight. If both A and B are given in quantities exceeding the minimum requisite to maintain weight, growth now takes place, becoming more active as the dose is increased up to a certain point. But the optimum requisite to promote growth is not very much larger than the minimum requisite to maintain weight. McCollum and Simmonds believe that it is easier to keep the animals in good condition even if very small quantities of A and B are given, than to keep them in good condition when any other factor of the diet is seriously reduced.

Aron [1045] showed that extract of carrots contains large quantities of B, but is inadequate as a growth-factor unless supplemented with A, which can be best done by adding a high-grade fat. Delf,[1115] who found that the expressed juices of green vegetables are rich in B, proved that these juices are not adequate growth-factors unless supplemented with A. She was able to demonstrate that when the dosage of B rises above the minimum, the growth-curve exhibits a rapid rise. But the optimal effect is soon attained, and beyond this point a further increase in the dosage of B has no influence on growth. Aron, and also Erich Müller and other specialists in the diseases of children, observed that in children that were supposed to be thriving, to supplement the diet by fresh vegetables, extract of green vegetables, extract of carrots, or extract of bran, could always bring about a further increment of growth. These observations show how defective the nutrition of our children must be in contemporary life, even under what appear to be favourable conditions.

Obviously, experiments of this kind must be subjected to a very rigid criticism, especially as regards the general environment of the experimental animals. In earlier days, before experience of these matters had been gained, experimenters were seldom able to breed healthy animals for several generations in succession. As late as 1916, J. C. Drummond [498] (whose statement was confirmed by noted German investigators) declared that it was impossible to bring up chickens properly under laboratory conditions, especially when the birds were fed on sterilised food. The belief gained ground that the activity of the intestinal bacterial flora must be essential to the life of the higher animals. But further study of the conditions of life and growth in various species of animals has shown that this assumption was erroneous. The ill success of the earlier experiments was mainly due to a destruction of the complettins in the animal's food by excessive sterilisation—by overheating. But, apart from this question of the food, many of the environing conditions are of vital importance. The animals must have room to move about naturally; the food-containers must be protected from defilement, and yet must be readily accessible;

there must be a sufficiency of light and fresh air, etc. Nor must psychical influences be neglected; the animals must enjoy the pleasures of society, and must not be needlessly disturbed. Merely taking them out of the cages frequently, in order to weigh them, may have an unfavourable effect on the growth-curve. Robertson and Ray [483] have paid special attention to such matters in experiments on mice, with excellent results.

One factor of great importance is the supply of a sufficiency of indigestible material to give bulk to the faeces—material now termed "roughage." Aron [448] drew attention to this in connection with nutritive experiments on rats; McCollum and Davis,[431] and McCollum, Simmonds, and Pitz,[507] in the case of omnivora; and Hart, Miller, and McCollum,[515] in the case of pigs and rats. Osborne and Mendel,[692] and Hart, Halpin, and Steenbock,[1260] were able to show that the debility of fowls fed under laboratory conditions could be completely cured by giving them a sufficiency of roughage. The best material for this purpose, better than charcoal or sand, is a chemically pure filter paper. Considerable quantities of this material are requisite; a hen needs about two-thirds of a square metre of thick filter paper every day.

Difficulties arose, at the outset, in preparing complettin-free proteins, and indeed in the composition of the diet in general. The first really decisive successes are recorded in a paper by Osborne, Mendel, and Wakeman [1098] published in 1920, when the physical and chemical properties of the complettins were fairly well understood. In a subsequent paper,[1331] Osborne and Mendel amplify their reports, making special reference to the preparation and administration of the individual complettins; but these prescriptions are less satisfactory than could be wished, for the authors do not draw an adequate distinction between the various water-soluble complettins.

It is worth repeating here that, even when the other environing conditions are all that could be desired, the validity of the results may be seriously endangered by the use of too small a number of animals. In this respect, likewise, Robertson and Ray's experiments on mice [484] deserve

the closest attention. These observers have recorded the average development of mice during the different stages of their life. Obviously a knowledge of such details in the case of experimental animals is of decisive importance in our appraisement of the results.

In conclusion, it is well to note that the tastes acquired by animals during the natural conditions of existence in the free state—their instincts, if you like to use the term—help to safeguard them against mistakes. Osborne and Mendel [739] record the observation that rats given a free choice between two food mixtures which appeared to be identical in respect of taste and physical qualities in general, instinctively preferred the mixture which was adequate; some of the animals that seemed to like a change of diet, and would not at first confine themselves to one or the other, concentrated their attention on the adequate diet as soon as growth began to be deficient.

b. Occurrence of B.

Whereas the complettin A is not very widely diffused, the complettin B is present in a large number of foodstuffs. The following whole grains and other seeds contain considerable amounts: oats,[625] maize,[578] wheat,[579] barley,[740] malted grain,[781] beans,[636] soy beans,[659, 665] earth-nuts,[681] pulses generally,[645] cotton seeds.[654] Cajori [1266] reports that to maintain growth in rats, 0·5 gramme of chestnuts, walnuts, or hickory nuts, 2 grammes of pine kernels, hazel nuts, or Para nuts, and nearly 3 grammes of almonds, were requisite. According to McCollum and Simmonds,[682] seeds in general contain large quantities of B, the husks and the brans being especially rich in this substance,[448, 730, 780, 781, 896] which can easily be extracted therefrom. McCollum, Simmonds, and Pitz,[507] and Osborne and Mendel,[873] state that the germs contain even more B than the bran or husk; but the cereals are least favoured in this respect. Bananas, according to Sugiura and Benedict,[775] and according to Langstein and Edelstein,[780] are so poorly supplied as to be an inadequate food; but the insufficiency manifested in these experiments may be referable to other causes. Aron [781] insists that fresh fruits contain plenty of B. Plums, pears, and apples,[1147] are not conspicuous in this respect; but cocoanut cake [872]

oranges,[1153] and lemons,[1147] contain large quantities; and according to Osborne and Mendel orange juice is as effective in this respect as fresh milk.

All observers are agreed [730, 780, 896] in describing cabbage as peculiarly rich in B; so are green vegetables in general.[781] According to Osborne and Mendel,[831] 1 gramme of the dried substance of lucerne or spinach contains as much B as do 2 grammes of wheat, soy beans, eggs, or milk; white cabbage, clover, and timothy grass are about equal to spinach. According to Steenbock, Gross, and Sell,[1053] and according to Osborne and Mendel,[1098] among the last-named, clover is the richest in B. Lucerne contains nearly as much, but the amount in spinach, tomatoes, cabbage, kohlrabi, carrots, and potatoes, is only half as great, and that in beetroots is even less—all measured in the dried state. The dried substance of 16 cc. of milk has the same efficacy as 1 gramme of dried spinach. According to Osborne and Mendel,[937] confirmed by Whipple,[1287] onions are fairly rich in B. So are turnips, mangel-wurzels, the leaves of the same, and tomatoes, very rich in B [937]; and according to Steenbock, Gross, and Sell,[981] in an artificial diet, 15 % of carrots, swedes, or the rhizomes of Arum maculatum (lords and ladies), will suffice to maintain normal growth; when sweet potatoes were used instead of the carrots, etc., 20 % was requisite; of sugar beet or of mangel-wurzel, even more was needed. Lecoq [1076] formulates what he regards as a general rule when he says that all the active tissues contain large quantities of B, whereas the storage tissues are comparatively ill-supplied with this substance. This is in conformity with the observation that wheatmeal [873] is rather poor in B; and that polished rice [454] and the finest cottonseed meal [524] contain so little that they are unable to promote normal growth. It is not surprising that, according to Osborne and Mendel,[937] grass should contain much more B than mature hay contains, for the latter is already on the downward path towards death at the time of reaping. McCollum, Simmonds, and Pitz [625] stress the fact that all natural fodders, which have not yet been subjected to artificial methods of preparation, are rich in B. We have seen, however, (and Steenbock, Gross, and Sell [981] are emphatic in asserting) that the quantity of

B in any natural nutrient cannot be regarded as a constant, for it varies according to circumstances.

The lower plants, likewise, are rich in B. Abderhalden [896] has shown that fresh yeast contains large quantities; and Langstein and Edelstein [730, 780] tell us that the richness in B is maintained by yeast in the dry state. Pacini and Russel [703] demonstrated that an extract of typhoid bacilli, and the culture medium in which these organisms had been grown, were rich in B; this throws a new light upon the frequently observed fact that after typhoid fever in children a rapid increase in stature is apt to occur.

Butcher's meat would seem, according to Osborne and Mendel,[663] to be very poor in B; but meat extract is rather more liberally supplied. Drummond [690] makes the same report as regards the muscular tissue of stock-fish, herring, and preserved salmon. The aggregate herring seems to be better supplied, and Drummond supposes that the difference is due to a concentration of B in the reproductive and other glands. But the same authority reports that in mammals the testicles, the ovaries, the pituitary body, the thyroid, and the thymus, are very badly supplied with B; and that in rapidly growing tissues, such as those of the foetus and of tumours, no B can be found. On the other hand the pancreas,[564] the liver, the heart, and the brain contain an abundance of water-soluble B.[662, 702]

Of exceptional interest, of course, is it to ascertain the B content of milk, the natural food of the growing organism. Both human milk [781] and cow's milk [737] appear to be rather poor in this growth-complettin. For rats, 16 cc. of milk are requisite to secure normal growth; when the allowance was limited to 15 cc., a supplement of 0·2 gramme of dried yeast induced a marked and sudden increase in growth. As far as the promotion of growth is concerned, it does not matter whether we give full milk, skim-milk, or Osborne's protein-free milk; approximately the same quantity of each of these is requisite. In the case of dried milk, the dosage must be about 50 % higher.[737] Be it noted that the last statement applies to the dried milk of transatlantic manufacture, which is much more sensibly prepared than the German brands. German dried milk probably contains very little B.

Since B, like D and the vitamins, is apt to be carried down as a precipitate with other substances, considerable quantities of B are often found in the casein and lactose of commerce.[499, 579] If, therefore, these substances are being used in experiments on growth, they must first be carefully purified.

But the B content of milk, like the B content of other natural nutrients, is far from being a constant. The investigations of Osborne and Mendel,[1131] Hopkins,[1314] and others have shown that the amount of B and also the amount of A in the milk vary according to the season and according to the nature of the fodder. The amount is largest during spring and summer, and when the animals are pastured or are given green fodder; in autumn and winter, and when the animals are stall-fed or are given dry fodder, the B content falls off.

c. Quantitative Estimation of B.

Williams,[923] and almost simultaneously Abderhalden and Koehler,[952] observed that the growth of yeast is notably stimulated by the addition of extracts "rich in vitamin." Bachmann [1229] and Williams [1145] independently proposed, almost at the same date, to make use of this fact for the quantitative determination of the amount of B in various nutrients and extracts; the method received the endorsement of noted investigators,[1205, 1284, 1297] and has been modified in several directions for the avoidance of irregularities. Bachmann [958] had himself pointed out that the growth of different stocks of yeast was very variously affected by such additions of vitamin-containing extracts; and Emmet and Stockholm [1203] observed that the reaction was inconstant when only one stock of yeast was under observation. Moreover, Lumière [1127] noted that the addition of well-defined organic or inorganic substances often produced better results than extracts rich in B; and also that extracts that were certainly devoid of complettin had, none the less, a powerful effect. Quite recently, Fulmer, Nelson, and Sherwood,[1372] have fully confirmed Lumière's observations; and McDonald and McCollum [1358] have drawn renewed attention to the familiar fact that a vigorous growth of yeast can be secured

in nutritive solutions containing little else than inorganic substances, and certainly no B. We must assume, therefore, that the stimulus to the growth of yeast provided by various extracts is little, if at all, dependent upon the presence of B. It follows that the deductions drawn by various authorities,[1286, 1287, 1298, 1371] upon the basis of such experiments concerning the B content of the most diverse nutrients and animal organs, are entirely fallacious. Those who wish to ascertain the quantity of B in any nutrient or organ must, therefore, have recourse, as of old, to the tedious and costly method of experiment on animals; but the results obtained by this method are trustworthy.

d. Properties of the Complettin B.

The growth-complettin B (which Abderhalden, in defiance of the fact that it contains no nitrogen, speaks of as "nutramin") is, by universal agreement, readily soluble in water,[448, 453, 454, 499, 654, 682, 730, 780, 1076, etc.] and therefore is completely removed from vegetable food by the customary practice of throwing away the water in which the vegetables have been boiled.[784] In contradistinction to A, it appears to be insoluble in fat [453, 454]; but like A it is soluble in alcohol in a moderate degree of concentration.[499, 1076] The latter statement appears to conflict with a report by Loeb and Northrop [569] to the effect that the efficacy of the substance as a growth-factor is "permanently injured" by alcohol. The growth-promoting substances are insoluble in acetone, ether, and benzin [1076]; but strangely enough can, according to McCollum and Simmonds,[670] be redissolved out of the alcoholic extract by benzin or by acetone after precipitation with dextrin and subsequent drying. No less strange is the observation of Robertson and Ray,[1296] that the growth-factor can be extracted from brain substance by acetone, and it seems questionable whether what really happens in this instance may not be merely the removal of an admixture of A by fat-solvents.

When we attempt to study the properties of the complettin B, we have to reckon with a very disturbing factor, namely that most authorities have failed to draw any distinction between B and D, this often leading to serious con-

tradictions. For example, nearly all subsequent investigators have confirmed the observation of McCollum and Simmonds [670] that this complettin is unaffected by hydrochloric acid, nitric acid, and sulphuric acid. But these same two American authorities, in the same paper, describe the complettin B as sensitive to alkalies—a statement which conflicts with the reports of most other observers. According to Byfield, Daniels, and Loughlin,[1153] the growth-factor in oranges will resist, not merely alkalinisation, but subsequent boiling for five minutes; while Whipple [1287] assures us that in cabbage it will tolerate boiling for several hours, even in a solution containing 0·1 % of hydrochloric acid or a corresponding amount of sodium bicarbonate. In like manner, a considerable heating of animal substances such as meat, during which ammonia is always formed, has no influence upon the water-soluble growth-complettin.

Speaking generally, this complettin, in contradistinction to complettin D, seems to be fairly insensitive to heat. An hour's boiling of meat, and even an hour's sterilisation of meat at 115° C.,[892] leaves B unaffected—though Richet [893] declares that an hour's boiling renders meat incompetent to maintain growth in the dog. As regards this last observation, however, the destruction of the complettin does not seem to be the cause of the failure of growth, for the dog was given nothing but meat, which is per se an unsuitable diet for a growing animal. According to the same authority, an equivalent amount of meat and bread can be heated to 100° without the process interfering in any way with the growth of a dog nourished on this mixture. The observation confirms the foregoing criticism of the previous one. The growth-complettin in brain tissue will tolerate three-quarters of an hour's heating at 130° C.,[892] but is somewhat damaged by an hour's heating at 135°. In beans it is unimpaired by boiling,[691] and will even tolerate boiling for six hours.[499] The boiling of heart, liver, brain,[702] milk,[1300] tomatoes,[899] potatoes,[773] and carrots,[784] has no effect upon the growth-promoting qualities of these nutrients. In polished rice, the complettin B is unaffected by ordinary boiling, but is somewhat damaged by one-and-a-half hour's heating at a temperature of 134° C.[970]

The drying of milk[969] and the pasteurisation of this fluid,[1131] have no influence; and prolonged heating at a very high temperature is requisite to destroy the traces of B in the casein of commerce.[562] Orange juice can be boiled until it becomes dry from evaporation[1147] without destroying the complettin; and the drying of carrots, potatoes, cabbage, turnips,[984] sliced potatoes,[773] or vegetables in general, at a temperature of from 50° to 60° C.,[1098] does not seem to weaken the growth-complettin in any way. Sliced potatoes have to be autoclaved for several hours at a temperature of 120° C. to produce a markedly injurious effect upon this complettin. In ordinary dried yeast, the growth-complettin is still fully efficacious. Even several hours' heating at 105° C. had no effect upon it.[568, 1058]

As we learned in Chapter Four, some authorities believe that the antineuritic D and the water-soluble growth-complettin B are identical, and others consider that this identity may be assumed with considerable probability[619, 1153, 1194]; but the respective reactions of these two substances to alkalies and to heat exclude the possibility of their being identical.[979, 1202] It is proper, however, to point out that, in experiments of this kind, trustworthy results can only be secured when steps are taken to ensure that during the heating process the temperature which is supposed to be operative shall be reached in the interior of the substance under treatment as well as upon its surface. During the customary process of sterilising masses of an experimental diet at a presumed temperature of 110°, 120° C., or more, the temperature in the interior of the mass will only rise (as in the baking of bread) to about 70° C. Portier and Randoin[935] have drawn attention to this source of fallacy, and have suggested a practical method whereby the error can be avoided. The experimental food is divided into small portions which are placed in muslin bags that hang freely in the interior of the sterilisation chamber; this will ensure that the whole substance shall be raised to the desired temperature. The experimenter must, however, be careful to place a saucer beneath each of the bags, to catch drippings, and these must be remixed with the food after the sterilisation, for otherwise grave errors may ensue.

Sugiura and Benedict [967] found that the growth-complettin B was rapidly destroyed by exposure to radium emanation.

According to Eddy,[564] the growth-vitamin is precipitated by phospho-tungstic acid in an acid solution, and Funk, as we have seen above, was originally of the same opinion. In a subsequently published paper (Funk and Macallum [563]) he inclines rather to the view that when the vitamins are being isolated by the phospho-tungstic-acid process, this substance is accidentally entangled in the precipitate. In this connexion, Drummond [619] has pointed out that any precipitate formed in a solution containing the growth-complettin tends to carry down the complettin with it.

We are led to infer that the growth-complettin must exist mainly in the form of a colloidal solution. The supposition is confirmed by the fact that the complettin, like so many other colloids, is absorbed by alumina.[564, 1043, 1153]

e. Physiological Effects of the Growth-complettin B.

One of the most striking symptoms in animals suffering from B deficiency is the almost invariable onset of gastro-intestinal disorder,[1056, 1239] which appears in adults as well as in growing animals.[1195] Experimenters were at first inclined to believe that the absence of the growth-complettin led to the formation of toxins within the alimentary canal; these were supposed to be absorbed by the organism. The theory was that the action of B was analogous to the action of the vitamins [563]—it was presumed to neutralise these toxins or counteract their effects.[515, 1146] I have already pointed out that earlier investigators were prone to attribute the ill-success of experiments, with sterilised diets to the absence of beneficial microbes.[783] It was natural, therefore, to assume that the growth-complettin had a favourable influence on the intestinal flora.[1046] Open to the same interpretation were the repeated observations [1055, 1116, 1195, etc.], that when the complettin B was deficient in the food the animals suffered far more from prostration and were more liable to infections of all kinds than the controls, which received an ample supply of B.

The general symptoms, however, were also accordant

with the assumption that the growth-complettin might in one way or another exert a direct influence on metabolism.[1224] But when Aron [1213] assumed that this influence might be exerted by the stimulation of peristalsis, he overlooked the fact that the B-containing extracts contained numerous other substances which had long been known to exert a stimulating influence on peristalsis. (Cf. Plant [1291].)

The increased power of resistance to infection on a diet containing an ample supply of B must, however, be determined by other factors than those which account for natural immunity in the ordinary sense of the term, for Zilva [917] reported that in guineapigs a lack of B had no effect on the amount of agglutinin and amboceptors in the blood; and that when the animals of one group were allowed free choice of food for six months, while the animals of another group were placed upon a restricted diet for the same period, no difference in the complement activity of the blood could be detected in the two cases. Obviously, the increased power of resistance when the diet contains a sufficiency of B must be the outcome of the general improvement in the nutrition, which enables the animals to resist noxious influences more efficiently than when they have become weak and sickly either from natural causes or through a diet artificially rendered inadequate.

Drummond [687] has published an observation which has not been confirmed by any other investigator, that when there was a lack of B in the diet the animals suffered from kreatinuria. This symptom must have been due to a general lack of bases rather than specifically to the lack of B, for, as I have repeatedly shown, a lack of bases almost always leads to an increased excretion of kreatin.

But the foregoing assumptions do not touch the cardinal point in the mode of action of the water-soluble growth-complettin. We have already learned that Funk was led in the first instance to assume the existence of this complettin by the striking observation that its absence from the food made the maintenance of weight impossible in adult animals, and the maintenance of normal growth impossible in immature animals. The first signs of a lack of B in the diet [1224] consist of arrest of growth, loss of weight, general

debility, and loss of appetite which may culminate in the absolute refusal of food. Nervous disturbances have sometimes been observed shortly before death. (Cf. Drummond [687].) They must probably be ascribed to the use of a diet deficient in D as well as in B; in that case they would be dependent upon the absence of the water-soluble antineuritic principle and not upon the lack of B.

The most remarkable point about the effect of B is, just as in the case of vitamin or of D, that very minute quantities can be shown to have an influence.[1058, 1060] When we find that the addition of as little as half a gramme of dried clover or spinach to the diet can render it competent to induce normal growth, we realise that the quantity of complettin requisite must be extraordinarily small.

When discussing the efficacy of A, we learned that both for this and for B the law of the minimum is valid. Drummond [687] points out that, within certain limits, the extent of growth is proportional to the amount of B in the food. The first result of the addition of B is shown in an increase of weight, this occurring also in adult and healthy animals [1224]; subsequently, in immature animals, vigorous growth speedily ensues. Simultaneously there is an improvement in the general appearance; if the tint of the skin has been morbid, a healthy colour is restored; in hairy animals, the coat becomes thick and glossy once more.[1248, 1268] But we must bear in mind the possibility that the latter phenomenon may be the outcome of the simultaneous administration of D.

Figueira [1046] noted that in sucklings extracts of wheat bran, when given in large quantities, were apt to induce diarrhoea. We have no reason to suppose that this symptom is due to the growth-complettin, for Abderhalden and Schiffmann [1273] have shown that B in watery extracts is absolutely non-toxic both in frogs and in mammals. Alcoholic extracts of bran gave rise to accessory symptoms, and especially to tonic contraction of the bloodvessels, which were not noted when watery extracts were administered.

The growth-complettin, however, has certain bad effects. As Funk pointed out, it may not merely affect the body and the organs favourably, but may also promote the growth

of tumours should these exist. Conversely, Hopkins has proved that in animals fed on a B-free diet, tumours grew to only about one-fourth the size attained by similar tumours in controls. Copeman, who reports these experiments, deduces from them a method for the treatment of cancer, and declares that he has secured good results by prescribing a diet poor in B. Mackenzie,[1055] in answer to this suggestion, has pointed out that Drummond's experiments have demonstrated the impossibility of starving the tumour without starving the host.

7. Behaviour of the endocrine Glands.

McCarrison [1240] has shown that the endocrine glands share in the general malnutrition. Nearly all of them undergo atrophy; but the adrenals are an exception, for when there is a deficiency of B they undergo hypertrophy just as they do when there is a deficiency of vitamin. The requirement of the endocrine glands in respect of B seems to be small, just like that of other organs; but their needs are so vital that they have the preference over the rest of the body as regards the utilisation of B. This is proved by an interesting experiment made by Stewart.[1201] He gave white rats so spare a diet for a period ranging from eleven to twenty-two days after their birth, that they did not put on weight at all from the time of birth. Nevertheless, the animals grew considerably in length; and the head increased in weight by about 45 % at the expense of the trunk and the extremities. Simultaneously, the increase in weight in the viscera amounted to 46 %, that of the skin to 25 %, and that of the muscles and bones taken together to only about 6 %. The most remarkable point was the behaviour of certain special organs. As compared with conditions in the newborn animal, the liver had fallen off by 23 % and the thymus by 49 %, whilst the thyroid, the ovaries, the lungs, and the adrenals, remained of the same weight as at birth. Some of the other organs had increased in weight, the increase in certain cases being enormous: the pineal gland was heavier by 21 %; the heart, by 26 %; the pituitary body, by 29 %; the stomach and intestines, by 40 %; the spleen, by 33 %; the spinal cord, by 83 %; the kidneys, by 90 %;

the brain, by 125 % ; the eyes, by 146 % ; the epididymes by 225 % ; the testicles, by 374 %.

This led Funk, as early as 1913, to the assumption that the action of the growth-complettin cannot be a direct one, but must be effected indirectly by a stimulation of the activity of the endocrine glands. Abderhalden [953] takes the same view. He regards the complettins as stimulants, each of which has a specific action upon certain groups of cells ; in one case, upon those of the digestive glands ; in another, upon nerve cells ; in another, upon the cells of the endocrine glands ; in another, upon the involuntary muscle of the intestine ; and so on.

It has, in fact, long been known that there are intimate relationships between growth and the activity of various glands. For instance, the reproductive glands, prior to the development of their reproductive functions proper, appear to form internal secretions which promote growth. We know of the thyroid secretion that it has a special influence in promoting growth ; on the other hand, hypothyroidism in youth leads to an impairment of the whole bodily development and to the most various disproportions and malformations. Very instructive in this respect are some of Abderhalden's dietetic experiments, notably those on tadpoles.

Especially important, in this connection, is the activity of the pituitary body ; this statement concerns the internal secretion of the anterior lobe, for that of the posterior lobe has no influence on growth. Consequently, Höchst's hypophysin [1296] has quite a different effect from the tethelin first prepared by Robertson and Ray from the anterior lobe. Tethelin is a well-defined chemical entity, having the composition of a β-imid-azolyl-ethyl-amine ; and its mode of action has been elaborately studied by Robertson and Ray in masterly fashion.[485, 486, 487, 548, 862, 863, 864, 865, 1141]

The most characteristic feature of the action of tethelin is that it stimulates the growth of the more active cells, and tends to inhibit the growth of connective tissue. Thereby the youth of the tissues is preserved, and a powerful influence is exercised upon the onset and the duration of sexual maturity and sexual functioning. The effects of tethelin vary greatly, according to the length of time for which it

is given, and according to the phase of life during which it is administered. When given continuously from birth onwards, it induces gigantism, but the giants thus produced have a short life. On the other hand, when tethelin is given only during early youth and then discontinued, it leads to increased growth, and the effect upon growth lasts beyond the period of administration; but the prolongation of the stage of youth thus determined leads, further, to a general prolongation of life. Generally speaking, these results have been confirmed by Marinus,[919] and by Abderhalden and Brammertz [1376]; in so far as there are differences between Abderhalden and Brammertz's results and those of Robertson and Ray, we have to remember that the experiments of the latter were performed on mammals, and those of the former on tadpoles. Almost simultaneously with the first experiments of Robertson and Ray, Clark [446] made investigations into the effect of the anterior lobe of the pituitary body on fowls. Not only did he note an enhanced growth in the birds, but he believed that their laying was favourably influenced. More recently, Simpson [1193] has experimented on the same lines, and declares that tethelin has no favourable effect upon laying. Larson [894] found that in thyroidectomised animals, tethelin had a favourable influence upon the general condition and increased the duration of life in the animals that had been subjected to this operation.

According to Popielski,[1322] tethelin, or rather β-imidazolyl-ethyl-amine, does not exist ready-made in the tissues, and is certainly not found in the anterior lobe of the pituitary body. On the other hand, he has found this substance in the stomach, and he assumes that it must be a decomposition product formed during the isolation of the real active body. However this may be, there can be no doubt that neither tethelin, nor the natural secretion of the anterior lobe of the pituitary body, represents the growth-complettin of which we are in search, for the effects of these substances differ too much from those of the growth-complettin. Moreover, when the milk of a lactating animal is deficient in B, and the growth of the sucklings is consequently below par, we cannot improve growth by adding portions of the anterior lobe of the pituitary body to the

maternal diet, whereas such improvement in growth promptly follows the administration of B to the mother.[657]

According to Robertson and Ray,[1141] cholin has a similar effect to tethelin upon subsequent growth; but cholin is even more destructive to life, for large quantities of cholin have to be administered. These are stored up in various organs and exercise a noxious influence. The effect of numerous other substances on growth has been studied. It has been found that hydrocithin [399] has a favourable effect on growth; and, on the other hand, that cholesterin [353, 530, 531] and lecithin [355, 530] tend rather to retard growth. No substance with a genuinely analogous influence to that of B has hitherto been discovered. The nature of B and its mode of action still remain to be elucidated, but there is one more point to which I must refer before leaving this subject.

B appears to have a peculiarly powerful influence upon the growth and the activities of the endocrine glands, for these glands (with the exception of the adrenals) atrophy when B is deficient. Now we have to remember that growth is the resultant of the interaction between the secretions of certain glands—some of which are known to act in this way, while the effect of other endocrine glands on growth perhaps still remains to be discovered. There are, therefore, considerable grounds for accepting a hypothesis put forward by Funk. He supposes that B cannot be synthetised in the body, and is therefore not (as we have found the complettin D to be) directly indispensable. B, suggests Funk, must be indirectly effective, by keeping the endocrine glands in good order and by stimulating their activity. Additional support to the hypothesis may be furnished by the observation that—though, in general, the growth of sucklings is dependent upon an adequate supply of B to the mother—in the absence of this, normal growth can be secured by the direct administration of B to the sucklings.

8. Importance of the Nutrition of the Mother.

The proper feeding of the mother from the first moment she conceives is of decisive importance to the growth of the offspring. The mother's diet even before she conceives is not without influence in this respect. We have, of course,

to reckon with a factor competent, in a measure, to correct even grave errors in the maternal diet—a factor but for which the animals we are pleased to term civilised human beings would long ere this have died out. I refer to the marvellous energy displayed by growing animal organisms in securing, even in the most unfavourable circumstances, the nutrients requisite for maintaining life and promoting growth. To a degree, moreover, a like energy is displayed by the mammary glands, the maternal organs which are mainly responsible for the wellbeing of the offspring during the period that immediately follows birth.

As regards the importance of diet even before conception, this has been clearly proved by the researches of Zuntz,[861] who found that an exclusive diet of protein and fat, or an exclusive diet of protein and carbohydrate, led in both sexes to grave impairment of the reproductive faculty. The animals conceived less frequently, and had smaller litters, although the individual offspring were normal in size, structure, and weight. Zuntz also found—as Röse [69, 70] had found more than ten years earlier—that a long-lasting deprivation of calcium has likewise a deleterious effect upon the reproductive powers, but that in this case the whole development of the offspring is seriously affected. In this connexion, I must refer once more to Urbeanu's researches, which showed that when the supply of calcium to fowls was restricted to an amount that seemed just sufficient for the maintenance of the maternal organism, sterility became apparent after three or four generations. McCollum and his collaborators, too, and also Osborne and Mendel, have frequently drawn attention to the importance of a proper diet to the integrity of the reproductive powers; and more especially do they stress the fact that the thriving of a single generation affords no guarantee that the diet is a satisfactory one. In many cases, the effects of an inadequate or an ill-balanced diet do not become apparent for several generations. Only then do we find that the animals conceive more rarely, and that the offspring appear more and more weakly, until ultimately complete sterility, or failure of the lacteal secretion, ensues.

If the mother's diet, though containing a sufficiency of

proteins, contains these in a form which is not fully adequate for promoting growth in the offspring, the maternal organism supplies the foetus with what is lacking by drawing upon the maternal store. Even inanition in the mother will not prevent reproduction, and the structure of the offspring seems perfectly normal, but Zuntz [861] states that the weight is below the average.

Insufficiency of the maternal diet in respect of protein has no effect upon the *composition* of the milk [246, 561]; Behre [1256] and Stern [1257] report that the inadequacy of fodder during the war had no notable effect on the composition of cow's milk. All authorities are, however, agreed that the *quantity* of milk falls off when the diet is insufficient.[1111] The long-continued malnutrition of nursing mothers that prevailed throughout Central Europe during the war, led to a reduction in the lacteal secretion. Ultimately, defective nutrition leads to a degeneration of the mammary glands, and changes in the composition of the milk then ensue.[1042] On the other hand, McCollum and Simmonds [1026] report that when the maternal diet is exceptionally high-grade, the secretion of milk is abundant, and the growth of the offspring is extremely active.

The faculty of the lacteal glands which enables them to extract from the maternal organism whatever is requisite for the production of normal milk, renders the mother's milk the best nutrient for the offspring during the early phase of life. Happily a conviction of this truth has gained ground in Germany of late, not only among doctors and governmental authorities, but also among women throughout the population. Bergmann [835] insists that even when the mother's milk is somewhat lacking in quantity, a breast-fed infant will thrive better than a baby sufficiently fed by hand.

The inorganic salts requisite for the formation of normal milk are likewise extracted with great energy from the maternal organism.[1026] Carl Röse,[69, 70] who experimented for a considerable period on goats, could not find that extensive variations in the diet produced any changes in the composition of the milk of these animals. But the mother cannot provide what she herself does not possess,

and ultimately therefore, when there is a persistent lack of inorganic salts in the maternal diet, the composition of the milk suffers. According to Hart and Steenbock [956] there then ensues grave debility in the sucklings.

The mammary glands also have the power of concentrating into the milk the growth-complettins A and B that are stored in the maternal organism, so that when these substances are deficient in the mother's diet, the milk will continue for a time to contain enough to promote normal growth in the offspring.[1026] Still, the influence of the maternal diet is marked in the case of both these complettins. Reference has already been made to the fact that in cows the amount both of A and B in the milk varies with the season and the fodder [1330]; the milk is only adequate for the maintenance of growth in the offspring when the maternal diet is itself adequate in this respect. Even in cases when the growth of the offspring is apparently taking place in normal fashion, we may find that the provision of an extra supply of B for the mother will be followed by a notable acceleration of growth in the sucklings.[561]

During weaning, and even later—when the young animals have become habituated to an independent diet, the mother's milk may continue to serve as a corrective for deficiencies in the diet.[1026] If any further emphasis of the importance of breast-feeding were requisite, and if anything could serve to persuade neglectful mothers to fulfil their duties in this respect, a general diffusion of knowledge concerning the work done during the last ten years upon this topic of the factors of growth would suffice. In Saxony, the State has recently instituted a special department for hygienic enlightenment, and it is eminently desirable that this new department should pay special attention to the spread of a knowledge of the foregoing facts.

9. Effect of the Inhibition of Growth upon subsequent Growth.

Another remarkable phenomenon must be considered before dismissing the subject of growth. As long ago as 1912, Osborne and Mendel [225] pointed out that when (for

one reason or another) the diet had been such as to check natural growth for a considerable period, normal growth was resumed as soon as the error in diet had been remedied. Among dietetic defects leading to an arrest of growth, these authorities allude to the following: [370] an insufficient supply of protein, or the lack of certain nitrogenous tissue builders; the lack of A or B; the lack of certain inorganic nutrients, or an improper ratio of these in the diet. In such circumstances, the inhibition of growth may be protracted far beyond the normal period of growth, and yet growth may even then be resumed when the noxious influence ceases to be operative.[370, 465] Thereby, the total duration of life may be considerably increased, and the animal may in the end attain its normal size.

Growth which is resumed after such an arrest proceeds at a more rapid pace than usual, attaining for a time a magnitude which is due to an excess of compensation. (Cf. Osborne and Mendel [225, 482]; Thompson and Mendel [715].)

Northrop [660] has published some interesting researches which corroborate the work of Osborne and Mendel. He found that such a temporary arrest and subsequent resumption of growth were actually followed by an abnormal prolongation of life—in the larvae of flies, for instance. But the prolongation affected only the phase of life subjected to the experimental modification. Thus, in these particular experiments, it was the larval period of life which was prolonged, whilst the life of the pupa and of the imago remained of average duration. It would seem, therefore, as if from this point of view the different stages represented different individuals.

In their first publication on the subject, Osborne and Mendel insisted that a restitution to the normal or an excess of compensation was only possible when the weight of the animal had at least been maintained during the period in which growth was suspended. Whenever the diet had been so inadequate as to cause loss of weight, the subsequent growth was inevitably impaired. Jackson and Stewart,[1059] who have substantially confirmed Osborne and Mendel's observations, nevertheless insist that when undernutrition has led to a temporary arrest of growth, the growth that

ensues after the defects in the diet have been made good is not fully adequate, so that throughout life the animals exhibit stigmata due to malnutrition during the developmental period.

An excellent idea of how important a satisfactory diet is to the wellbeing of children can be derived from a report made by K. B. Rich [1241] concerning the work of the educational authorities in the Chicago elementary schools. Investi gation showed that the treatment of tonsillar hypertrophies, carious teeth, adenoids, and flat-foot, was almost ineffective, although great expectations had been formed. What proved decisive for physical wellbeing was cleanliness, light, fresh air, exercise, and, above all, attention to diet. When these environing conditions were improved, there was a concurrent increase in weight and stature.

10. Summary.

We may sum up in a single sentence what has gone before by saying that normal growth is preeminently dependent upon a rationally composed diet. Children must be given a sufficiency of food, and the protein must be as high-grade as possible. From this point of view, potatoes and milk are the best; cereals are less suitable, unless the inadequacy of their proteins is made good by giving milk in addition. The diet must also contain a sufficiency of complettins: A can most advantageously be provided in the form of milk, butter, or spinach; fresh vegetables and fruit in abundance are a satisfactory source of B. The diet should contain from five to seven times as much of vegetables, potatoes, and salt-rich fruit (apples and pears are poor in this respect), as of meat, eggs, or cereal products—for otherwise an adequate excess of bases cannot be guaranteed. Care must be taken that the nutrients shall contain enough sodium and calcium, the latter being especially important. The sodium content must be at least one-fifth of the potassium content, and the calcium content must be not less than five times as great as the magnesium content. The latter requisite is sometimes difficult to fulfil; in regions where the water is poor in lime, it will be indispensable to give about three-quarters of a pint of milk daily.

Before I close this chapter, I must say a few words about the feeding of children in Germany and Austria during the war. The conflict brought tragedies enough in its train, but the matter we have now to consider was one of the most tragical of all. It has been proved that, in German Austria and in Germany, approximately one million children perished directly or indirectly from wartime feeding, and that almost all the children who survived were more or less seriously injured by the inadequacy of the diet. Perhaps the worst feature of the case is that the blame for what happened can only be indirectly ascribed to the blockade, for the chief factor was the stupidity of the German dietetic experts and of the government that acted on their advice. I repeatedly drew attention, both by word of mouth and in writing, to some of the grave errors that were being committed; but my remonstrances had no effect, and it is but a poor and belated satisfaction that the results of the British, American, and international commissions of enquiry have shown my criticisms to have been fully justified.

Consider, first, the most outrageous of all the errors of wartime feeding—the crazy, the utterly inexcusable, slaughtering of milch-cows in order to secure a few paltry pounds of meat. To attain this lamentable result, and to stop the mouths of clamorous flesh-eaters, our precious herds were destroyed. In the most short-sighted fashion, milkers were butchered each of which within a single year could have produced its own weight of invaluable nutrients in the form of milk, and no one stopped to think that thereby it was being made impossible either to breed for the future supply of meat or to provide for the subsequent victualling of the people with butter (rich in A) and with milk (rich in A, B, C, and inorganic salts). (Cf. Mason [1011].) Almost as bad was the potato control, whereby the price of one of our most important articles of diet was fixed at a figure at which it did not pay the farmers to grow the tuber. But, apart from these two errors, which are at least easy to explain, I have to think of two others which can only be described as criminal: the removal of the germ from cereal products; and the steaming or scalding of vegetables for conserves.

It has long been known that the highest-grade protein

in every grain, and nearly all the fat of the grain, are concentrated in the germ. Nevertheless, there was no hesitation about extracting the germ of the grain in the milking process in order to use the fat thus secured for the feeding of the already over-rationed munition workers. It was supposed that the germs, after the removal of the fat, were to find their way back to the community-at-large in the form of meal for breakfast use. I have never been able to learn what really became of them. In actual fact, throughout the war, we received at Weisser Hirsch on two occasions only a ration of a germ-containing meal, each person having about enough to make a small cup of gruel. One excuse given for the removal of the germ was that the keeping qualities of the flour were thereby improved—but these keeping qualities were of very little importance, seeing that we were all forced by hunger to eat our rations with the least possible delay. Besides, the statement is untrue. The whole procedure was a robbery of the energies of the German nation and a crime against our growing youth.

Even more serious, if possible, was the second error, the bleaching of vegetables before they were dried. In a subsequent chapter, this will come up again for fuller consideration, and it will suffice to say here that the mere steaming of vegetables for five minutes dissolves out so large a proportion of the inorganic bases that the residue contains an excess of acids. Simultaneously, the vitally important complettins are almost entirely dissolved out of the vegetables.

Chick [1237] and Dalyell,[1238] and also Block [1282] (a German investigator), in their studies of wartime diets in Germany, insist that the worst feature was the impoverishment of the food in respect of A, B, and C. British doctors and physiologists [1055] are unanimous in the opinion that the main cause of this defect was the method of preparing vegetables. The before-mentioned authorities record a number of striking instances in which severe attacks of scurvy in children were promptly relieved by the addition to the diet of carrot juice or raw spinach, or in some instances of butter or of codliver oil.

Among German medical practitioners, there are some who have long been aware of these facts, and have turned their knowledge to practical account. Above all, I must

refer to the work of Erich Müller and his collaborators, and to that of Aron, who, in the circles entrusted to their care, were able to secure admirable results with the scantiest of means. Block, too, showed that in severe cases of malnutrition in children, the addition of fresh vegetable juice to a milk and vegetable diet gives excellent results.

These views of mine, which to some extent had been advocated earlier by Lahmann, are now being widely trumpeted as a brilliant foreign discovery. It may be hoped, therefore, that even the Germans will at length break the shackles of tradition; and that, even in Germany, a current of fresh air will invigorate the science of dietetics.

Addendum to Chapter Four: Sprue.

a. Clinical Picture.

Among European residents in the tropics, especially in the East Indies and in the Sunda Islands, there frequently occurs a remarkable disease known as sprue or psilosis. It has not hitherto found a satisfactory place in the nosology. In the account I propose to give of this disorder, I am guided chiefly by the description given by Brugsch and Kraus, *Handbuch der allgemeinen Therapie*, section on Tropical Diseases. The illness begins with slight gastro-intestinal disturbances, which have nothing characteristic about them, and come and go. From time to time, isolated patches of inflammation appear on the tongue, to disappear again completely. In the course of years, the attacks grow more frequent, and the inflammatory manifestations on the tongue become more severe and last longer. When the disease is fully established, the inflammatory foci on the tongue gradually spread until they coalesce. The lingual epithelium disappears, and on the inflamed surface can be detected very small suppurating vesicles or extremely sensitive circumscribed minute ulcers. Thus in course of time the surface of the tongue is to an increasing extent denuded of epithelium; the mucous membrane is dry and fissured; the papillary body has vanished, the papillae being replaced by overgrowths of connective tissue. The whole musculature of the tongue has atrophied, so that the organ has become

extremely small, deeply furrowed, and thin. The gums and the rest of the buccal mucous membrane may be sympathetically affected with inflammation; the suffering may be further increased by salivation, or the secretion of a tenacious mucus, or sometimes by dryness of the mouth. The sense of taste is greatly impaired; the saliva has become acid, and the sulphocyanate may have completely disappeared from the secretion.

Inflammations of the rest of the upper part of the alimentary tract complicate the clinical picture, leading to difficulty in swallowing, pain on swallowing, a sense of fullness, flatulence and eructation, heartburn, and, in exceptional cases, vomiting. Although in the early stage of the affection the appetite is often excessive, it subsequently falls off, with the onset of achlorhydria. Burning thirst is common; the abdomen is in a state of flaccid distension. Borborygmi, and the rapid onward movement of the intestinal contents, show that excessive fermentation is going on. Colic is, however, present only in acute exacerbations of the disease.

The bowels act especially during the morning hours, and the evacuations may number ten or more, though they are sometimes suppressed for a while. The stools are generally of the consistency of pap, foamy, yellowish white in colour ranging to grey or greenish, though there is no sign of jaundice. Their reaction is acid. They contain an excess of fat, but no mucus or blood.

At a comparatively early stage the liver is reduced in size, but this may be no more than an outcome of the general atrophy. There are no special symptoms showing any involvement of the respiratory, circulatory, or urinary system. The urine sometimes contains an excess of bile-pigments; and when the stools are suppressed, indigo can be detected in the urine.

There is extreme emaciation; the skin becomes flaccid and wrinkled; ultimately death occurs in a condition of cachexia in which the patient has come to look almost like a mummy.

b. Pathological Anatomy.

Generally speaking the blood seems normal in sprue; but in severe cases, owing to the malnutrition, intense

anaemia ultimately sets in, so that the haemoglobin richness of the blood may fall to 40 % of the normal, or even lower. In the worst cases, the blood may come to resemble that of patients with progressive pernicious anaemia. But, apart from these extreme instances, the characteristics of the blood are those resulting from chronic toxaemia and from a plastic inhibition of haematopoiesis.

The pathological anatomy of this disease does not furnish any etiological explanation, for the pathological changes are no more than the results of the abnormal fermentations in the intestine. In the ileum there is a flaccid distention; the villi of the mucous membrane have atrophied and almost disappeared; thus the wall of the gut may be transparent and as thin as paper, unless thickened by oedematous infiltration. There are numerous punctiform ecchymoses, sometimes larger extravasations of blood, and bile-stained patches; these changes give the bowel a remarkable motley aspect. The oesophagus and the stomach are always affected, the coats being in most cases thickened, inflamed and infiltrated, or selerosed. The mucous membrane is wrinkled, thickened, here and there atrophic, and often flecked with haemorrhages. The mesenteric glands are enlarged and strongly pig-. mented; or, in some cases, atrophied and cirrhotic. The irritation of the bowel may spread to the peritoneum, leading to local peritonitis and the formation of adhesions. There are no marked changes in the bone-marrow, which is, however, greatly lacking in fat. The other organs all manifest the effects of the general atrophy.

c. Prognosis.

In advanced cases, the prognosis is unfavourable, and even in the early stages it is dubious. A cure will in any event take a very long time, and will demand, during this period and afterwards, from a seriously debilitated sufferer, the display of a great deal of patience, tenacity, and energy. In slighter cases which come under treatment at an early stage, the conscientious carrying out of the prescribed course of treatment may affect a cure; but relapses will only be avoided by extreme caution on the patient's part.

d. Treatment.

Rest in bed is needed only in severe cases. The main thing is to promote improved nutrition, by checking fermentation through reduction of the carbohydrates in the diet, and by lessening the putrefaction of nitrogenous substances within the bowel by restricting the supply of protein—thus securing a better utilisation and absorption of the food. Fat is very badly borne. A milk diet is generally the best, the milk being given unboiled, and it must not be too rich in cream. We shall do well to dilute the milk with Vichy water; if it is not borne even then, the effect should be tried of using an even more strongly alkaline water, such as Ems, for the dilution. Remarkable results sometimes follow the giving of fresh raw fruit, especially strawberries, but also bilberries and gooseberries. By degrees attempts may be made to increase the amount of protein in the food. Potatoes are well borne. When medical experts in tropical diseases assure us that vegetables cannot be tolerated, and most often be withheld for many years, we presume that we are once more encountering the fallacy which has now happily become obsolete as regards the treatment of gastric and intestinal disorders in general. But it is certainly of the utmost importance that anyone who has suffered from sprue should for years to come shun strongly-spiced, rich, or fatty articles of diet; a single indiscretion of this kind may prejudice the whole course of treatment.

e. Etiology.

As I have already shown, medical science is groping in the dark where the question of the etiology of sprue is concerned. It is certainly presumptuous for a person like myself, not being a practitioner of medicine, to express an opinion on the matter; but I feel nevertheless that my knowledge of the way Europeans feed in India, in conjunction with my special experience of modern theories of nutrition, will perhaps enable me to give some pointers.

First of all it must be remembered that, as far as diet is concerned, European life in India is about as unnatural as can possibly be conceived. The British have taken with

them to the east their national preference for a meat diet, and have wedded it to the indigens' taste for highly seasoned rice. The burning thirst induced by such a diet is slaked by vast quantities of iced and usually sweetened drinks (alternating with tea), which are frequently loaded with large doses of alcohol.

Naturally this regimen is extremely injurious to the gastro-intestinal tract. In the United States, too, iced drinks are greatly in vogue, and we are informed that the practice of consuming these beverages is found to be most unwholesome, giving rise in the first instance to acute disturbances, and subsequently in many cases to grave chronic disorders. The excessive stimulation of the mucous membrane is aggravated in India by pungent curry, and usually in addition by tobacco and alcohol. How can we expect the unfortunate mucosa to tolerate all this without inflamimatory reaction? Now, we know that gastric disorders frequently affect the condition of the buccal mucous membrane, which becomes thickened or inflamed, often with the formation of aphthous ulcers.

The wonder really is that cancer is not more frequent in tongues that are so much maltreated. Perhaps the reason is that, as previously explained, for the development of malignant tumours there is needed an abundant supply of B—this substance being so thoroughly utilised that the tumours are themselves free from B. In actual fact, the diet of Europeans in India, where fruit is scarce, is extremely poor in B; and this scarcity may account for many of the symptoms of sprue. First of all it may account for the readiness with which the buccal mucous membrane—which in general is so resistant and has such remarkable powers of regeneration—becomes inflamed and ultimately atrophies; and the same remark applies to the mucous membrane throughout the gastro-intestinal tract. We may suppose that the deficiency of B leads, not merely to a lowering of the capacity for resistance, but also to a grave impairment of regenerative power, so that inflammation that has once originated tends to persist indefinitely.

There can be no doubt, moreover, that the excess of acids in the food plays a notable part in the etiology; the

acidity of the saliva suffices to prove this. As to the part played by the metabolism of inorganic salts in the causation of sprue, nothing definite can be said in the absence of detailed investigations. It is noteworthy, however, that the nutrients recommended for the treatment are all characterised by excess of bases and richness in calcium. The effect of fruits in this respect must be conspicuous, for we should have anticipated that the skins and pips of the fruits found helpful would have irritated the bowel quite as much as any vegetables.

The fact that vegetables are not well borne is, of course, partly explicable by the irritant effect of the indigestible residues. But there are many vegetables which are fairly well borne in sprue—for instance, young spinach and young carrots, both of which resemble potatoes in leaving comparatively little irritant residue. It is, therefore, not easy to understand why potatoes should be so much better tolerated than vegetables in general. The difficulty is all the greater seeing that vegetables in general are poor in carbohydrates, whereas potatoes consist so largely of carbohydrates, and yet one of the main points in the treatment of sprue is to restrict the supply of carbohydrates. May not the explanation of this apparent contradiction be found in the fact that most of the other sources of carbohydrate are cereals, which contain a notable excess of acids, whereas potatoes are rich in bases? We shall be the more inclined to accept the explanation when we remember that by the customary methods of what is regarded as refined cookery, vegetables are robbed of their excess of bases, and that this may be the main reason why they are badly borne in sprue.

Such a theory is supported by another consideration. Milk contains only a slight excess of bases; and yet (at any rate in the early stages of sprue) it is not well borne unless its excess of bases is increased by dilution with mineral waters containing liberal amounts of bicarbonates, i.e. of alkaline salts.

The favourable effect of fruits can perhaps be explained by their C content, seeing that milk is rather poor in C. Perhaps the frequency of haemorrhages in sprue is referable to C deficiency, and it may be that closer examination

(especially in post-mortems, when attention has been directed to the point) will show further signs of masked scurvy. I make the suggestion with all reserve. In any case, fruits may furnish a welcome augmentation of the calcium supply, for the calcium content of milk seems to be inadequate in the long run for adult human beings.

As far as the widespread atrophy of the organs is concerned, the main cause of this is doubtless the general failure of nutrition consequent on the digestive disturbances. But when there is defective nutrition because the diet is quantitatively inadequate though qualitatively adequate, we find general atrophy differing from that characteristic of the deficiency diseases in that the glands continue to function. In the acomplettinoses, on the other hand, impairment of glandular functioning makes itself apparent at a very early stage. We have seen that this is especially characteristic of a lack of vitamin, of B, and of D ; and the early onset of slight acidity in sprue suggests an inadequacy of the diet in one of these respects. A survey of the foregoing considerations enables us to infer that the lack is not one of vitamin or of the antineuritic D, but that B is probably lacking.

It would be of equal value to suffering humanity and to scientific medicine if the problem of sprue were to be reconsidered with the aid of the modern methods of dietetic physiology.

CHAPTER SIX

THE FAT-SOLUBLE COMPLETTIN A

1. History; its Isolation.

In the previous chapter, when discussing the determinants of growth, it was necessary to consider some of the peculiarities of the complettin A in order to fill in our picture of the growth-factors. But the effects of the complettin A on the animal organism are not restricted to a favouring in growth; they are so multiform that a special chapter must be devoted to the fat-soluble complettin A.

The starting point in the study of the fat-soluble complettin was the paper published by Wilhelm Stepp,[93] a professor at Giessen, in the year 1909. He observed that a diet which had previously been quite adequate, proved after extraction with ether and subsequently with alcohol incompetent to maintain growth in mice and to keep the animals alive. If the solvents had been used hot, the readdition of the ether extract and of the alcohol extract did not make the diet adequate. If, however, the alcohol extract had been made with cold alcohol, the return of this extract restored adequacy to the diet.

The report seems to have been overlooked, for otherwise it would surely have led to further and more detailed investigations. A second report by Stepp,[234] published in the year 1912, also failed for the time to attract attention. In this instance Stepp showed that the active substances were not very resistant to heat; they were completely destroyed by two days' boiling of an alcoholic solution, or by boiling the whole food in alcohol for forty-eight hours, or by prolonged boiling in water. At that date, Stepp was inclined to regard them as lipoids. When a food had been rendered inade-

quate by such treatment, its adequacy could be restored by the addition of an extract made with cold alcohol from other portions of food. It was manifest, therefore, that the organism of the mouse was incompetent to synthetise these substances, and this led Stepp to infer that the lipoids were absolutely essential constituents of food. Two years later, Stepp supplemented his work with a report [396] showing that the denatured food could not be rendered adequate by the addition of pure fats. But the addition of various lipoid compounds was likewise found ineffective in this respect. An alcohol and ether extract of yolk of egg was, however, extremely active, so that Stepp continued to regard a combination of vitamins with certain lipoids as the active principle. The view seemed to him to be confirmed when he was able to prove [526] that the denaturation was effected mainly if not exclusively by the alcohol extraction and not by the ether extraction; and to show that the denatured food would be rendered adequate by an acetone extract of yolk of egg, and much better by an alcoholic extract of yolk of egg made subsequent to extraction with acetone. In some instances, the acetone extract was inactive whereas the alcoholic extract was effective. Vitamins alone, and various lipoid compounds, were ineffective; the combination of vitamins and brain lipoids was effective in certain instances.

The investigation did not enter the right track until Hopkins and Neville [267] noted in 1913 that the artificial diet employed by Osborne and Mendel could only maintain weight in mice for a limited period, but that when 2 cc. of fresh milk were added to the food (a supplement which increased the total dried substance by only 4 %) the mice remained perfectly well-nourished. This observation was confirmed by Osborne and Mendel.[295] They found that on the artificial diet, as originally supplied, rats could be kept going for a considerable period, even with increase of weight and a moderate amount of growth; but ultimately growth ceased, the weight fell off, and the animals perished. If, however, during the critical period a little milk or butter were added to the experimental diet, the rats quickly recovered, and normal development ensued.

Shortly afterwards, Osborne and Mendel [305] supplemented

their previous observations by finding that fat-free milk, and also the salts contained in the water of butter, were quite ineffective; but that perfectly pure butter fat, obtained entirely free from nitrogen and phosphorus by melting and centrifuging the butter, was a very active growth-factor, greatly superior to lard. This report was promptly confirmed by McCollum and Davis [386]; and Osborne and Mendel [350] were able to detect the active principles in the fat of yolk of egg and in codliver oil, but could not find it in almond oil.

Opposed to these reports was one made by Dezani,[389] who found that he could keep his experimental animals alive and in good condition on a lipoid-free diet, provided only that the diet were sufficiently varied. He contended that what was wrong with Stepp's experiments was that the monotony of the diet had induced loss of appetite in the animals subjected to experiment. We know to-day that Dezani's inferences were fallacious to some extent, inasmuch as his experimental diet, though free from lipoids, was not free from the complettin A. Almost simultaneously with the Italian's paper there came from two widely divergent sources confirmations of Stepp's observations. Kawashina,[427] and McArthur and Luckett [419] who reported along almost precisely the same lines, were able to show that the various lecithins, other lipoids, cholesterins, and fats, are not essential to life in mice [this is true, provided that the supply of protein is adequate]; but that, on the other hand, a diet consisting of casein, starch, lactose, lard, and milk salts, incompetent per se to maintain life in mice, could be rendered fully adequate by the addition of a substance present in yolk of egg and soluble in alcohol and ether.

An investigation made by Funk and Macallum [374] showed that the life-sustaining substance could not be identical with butter fat, for the addition of a thoroughly purified superheated butter fat could not render adequate a diet lacking only in the one factor under consideration, whereas the alcoholic extract made from the original butter was perfectly competent to render the diet adequate. Halliburton [738] therefore considers that the reason why fats are indispensable to life is that they contain this growth-complettin.

Nevertheless, as we learned above, a large number of other investigations had shown that there is another factor, the water-soluble complettin B, no less indispensable for the maintenance of life and growth. Since there is little of this complettin in fats, or none at all, it was natural to suppose that green vegetables, etc., were to be looked upon exclusively as the providers of B, and that A was present only in fats. Hence the two substances have been frequently confounded (cf. 714). But it soon became apparent that certain nutrients that were unquestionably rich in B, could only maintain growth when supplemented with A; and that others, such as green leaves, though free from fat, were adequate growth-factors without any addition of A.[1135]

By a large number of investigations it has now been proved beyond dispute that for the maintenance of body-weight and for the promotion of normal growth both A and B are essential.[453, 454, 874, 884, 1045] More especially has this been demonstrated by the work of McCollum and Simmonds,[661, 664] who simultaneously showed that both the growth-complettins were subject to the law of the minimum.

2. Occurrence.

The occurrence of A was first definitely proved in milk, and its presence in this fluid has subsequently been confirmed by numerous investigations.[225, 267, 295, 305, 386, 781, 1119] With the separation of the cream, the greater part of the A factor passes away into this [295, 305, 350, 386, 424, 781, 1146]; and when the cream is made into butter, the A is chiefly stored in the more fluid portion, the so-called butyric oil [305, 424, 477]; but considerable quantities of A remain in the skim-milk, and when the casein is precipitated they are included in the precipitate. Both the casein of commerce, and also cheese,[714] therefore invariably contain A, though in small quantities, so that neither casein nor cheese must form a component of an A-free diet. Yolk of egg, the first source of nutriment for the growing bird embryo, is very rich in A, for the fat of egg-yolk contains A in a concentrated form.[350, 526, 781, 1119, 1146] In the normal body-fat of animals, in beef fat for instance,[424, 618, 752] there are also large quantities of A, which, as in the case of butter, are stored in the ingredients

of the fat that have a comparatively low melting-point (the so-called oleomargarine or olein [424, 618, 752]); whereas the stearin of animal fat, just like the part of the butter which has a high melting-point, is practically free from A.[424] Consequently animal margarine, which is manufactured from oleomargarine or olein, is comparatively rich in A.[618, 1329]

In contradistinction to the normal body-fat, the storage fat of animals contains very little A.[752, 1223] For this reason, lard is very poor in A; [305, 374, 386, 424, 453, 454, 781, 1327] but it is not, as was at one time believed, completely free from A.[1146, 1326]

The fat of fish, like the fat of mammals, is rich in A, so that fish oils in general contain an abundance of this complettin.[690]

Passing to consider the individual organs, we find that the pancreas, the thymus, and the adrenals, contain comparatively little A [922]; whereas the kidneys contain more, the heart still more,[436] and the liver most of all. Consequently the oil expressed from pig's liver is as vigorous in its growth-promoting qualities as butter [702]; and at an early stage in this investigation codliver oil was recognised as preeminent among fats for its richness in A.[350, 374, 634, 781, 1146]

In contradistinction with eggs, the seeds of plants usually contain too little A to ensure the maintenance of normal growth. In especial this has been proved as regards oats,[625, 714] wheat [436, 515, 682, 714], barley [740], rye [714], and maize [436, 578, 658, 682, 714]. According to Steenbock, Boutwell, Gross, and Sell,[1027] yellow maize is an exception, for 88 % of this in the food suffices to maintain growth in young rats. McCollum and his collaborators,[578] however, found that the A content of yellow maize was inadequate to promote growth in pigs; but normal growth could be ensured in these animals if the maize were supplemented by an alcoholic extract from another portion of the same maize, this increasing the A content a little. Speaking generally, the cereals are inadequate [490, 682]; the germ contains a good deal more A than the endosperm and the bran,[436, 490] but not nearly enough.[507] Beans are very poorly supplied with A,[636, 658] this statement applying to soy beans [659, 665] and earth-nuts [681, 1169]; but there are certain pulses that contain fairly adequate quan-

tities.[645] Brazil nuts, butternuts, Barcelona nuts, walnuts, and almonds, are all poor in A; in like manner, almond oil,[350] olive oil,[781] nut oil,[752] cocoanut oil,[752] and cocoanut cake, are incompetent to maintain growth.[872] Cotton seeds are poor in A [524, 714]; and so, therefore, is cottonseed oil.[648, 1146] Since cottonseed oil and cocoanut oil are the chief constituents of vegetable margarines, these likewise are inadequate as growth-factors.[618] On the other hand, linseed, millet, and hemp seeds,[682] are reported to be fairly rich in A, although the quantity is inadequate.[714, 812]

Fruit would appear in general to be very poorly supplied with the fat-soluble growth-complettin. Especially is this reported of bananas,[775] oranges,[1168] lemons, and grape-fruit.[1147]

In respect of A content, seeds contrast with leaves which are, generally speaking, rich in A.[714, 1119, 1194] Thus, lucerne,[490] white cabbage,[490, 831] and especially green cabbage,[806] spinach, clover, and timothy grass,[831] are described as very rich. Quantitative data are given by Steenbock, Gross, and Sell,[1053] who tell us that 5 % of lucerne, clover, spinach, and artichoke leaves, or 10 % of white lettuce, in the food, will suffice to ensure normal growth and reproduction in rats; but even 15 % of white cabbage proves inadequate. Osborne and Mendel [1132] found that tomatoes were more active than an equal weight of butter fat, and that clover, lucerne, grass, and spinach were no less active. Dried white cabbage was less active.

As regards root crops, potatoes proved quite inadequate in this respect [777, 812, 981, 1132]; but the sweet potato, the American rival of the potato, was just as active as the extremely active carrot.[981] According to Zilva,[1150] carrots are richer than white cabbage; but Steenbock, Gross, and Sell found that turnips, mangel-wurzels, sugar beets, Arum maculatum (lords and ladies), parsnips, and common beetroot were quite inadequate.[981]

3. Complettin A and Lipochrome.

We see, then, that although the complettin A is soluble in fat, the amount of this substance in various nutrients is by no means proportional to their richness in fat.[490] At an early stage in these investigations, the opinion gained ground

that there was a definite ratio between the A content and the lipochrome content of food, the belief being that the nutrients richest in lipochrome were also richest in A.[1027] Carrots, which are among the most highly coloured of the root crops, are especially rich in both A and lipochrome.[784, 981, 1027] The careful investigations of Rosenheim and Drummond [1136] have shown, however, that although there is a general parallelism in the A content and the lipochrome content of nutrients, the parallelism is not invariably sustained :—

Foodstuff.	Lipochrome Content.	A Content.
Milk Fat	+ + +	+ + +
Yolk of Egg ..	+ + +	+ + +
Codliver Oil ..	+ + +	+ + +
Whale Oil	+ +	+ +
Beef Fat	+ +	+ +
Kidney Fat ..	+ +	+ +
Maize	+	+
Wheat Germ ..	+	+
Cabbage	+ +	+ +
Spinach	+ +	+ +
Carrots	+ +	+
Chicken Fat ..	+ +	+ +
Liver	+ +	+ +
Herrings	+ +	+ +
Cottonseed Oil ..	+ +	—
Cod	—	—
Lard	—	—
Cocoanut Oil ..	—	—
Hardened Fats ..	—	—

The hardening of fats seems to destroy the growth-complettin A ; and when fat is extracted with benzin or with ether, most of the complettin is removed by the process.[1140]

Just as in the case of water-soluble B, so also in the case of fat-soluble A, the richness of the natural nutrients is inconstant. In especial, this has been proved as regards milk and butter by Steenbock, Boutwell, and Kent.[752] These authorities suppose that the chief cause of the variations must be the different feeding of the cows, but it appears that the same fodder will contain different amounts of A at different times. Consequently, in the case of fat-soluble A as in that of water-soluble B, we have to reckon with

seasonal variations in the richness of the pastures. Furthermore, as we are about to learn, when dried fodder is in question, prolonged storage of the fodder is attended with a decline in the A content.

4. Relationship to other Complettins.

Among the descriptions of the properties of the complettin A we find several inconsistencies, which might lead us to suppose that we really had to deal with different substances in the different nutrients. A more careful examination shows, however, that the inconsistencies are mainly due to the great comprehensiveness of the researches concerned with the complettin A, and that in some of these there has been confusion with the other complettins—more especially with the complettin B. In the early stages of the investigation, the inclination was to regard A as a lipoid, and we have already learned that this was Stepp's original opinion.[526] But Osborne and Mendel [305] have proved (cf. also [714, 875, 1308]) that the substance must be free from nitrogen and phosphorus, or that if it contains either or both, it must do so in quantities that are almost incredibly minute; obviously, therefore, it cannot be a lipoid. As regards other ingredients of the fats, subsequent investigations [781, 875, 876] have shown beyond dispute that A is not glycerine, that it is not a saturated or unsaturated fatty acid, and that it is not an undecomposed fat; nor can the various sterins be accounted possible incorporators of the A influence. In the foregoing chapter (p. 204), we learned, indeed, that the sterins had the opposite effect to A, inasmuch as they interfered with growth, especially when given in excess. Funk [375] was at first inclined to believe that A must be a base having a similar action to that of the vitamins. But Stepp has given adequate proof,[517] first of all that A contains no nitrogen, and secondly that its mode of action is quite different from those of the vitamins; Funk and Macallum have confirmed this view.[464] The researches of Rosenheim and Drummond [1136] have shown that A, despite its kinship with the lipochromes, is not itself a lipochrome; and this has been confirmed by numerous authorities.[785, 959, 960, 961, 1170, 1313] It remained to be demonstrated that A and B were distinct.

The distinction is, in fact, obvious, for we know of substances (like butyric oil) which contain A and hardly any B; and of others (turnips, potatoes) which contain B and no A. Furthermore we find that A without B or B without A does not suffice to render a diet adequate; also, that the effects of the two differ greatly in certain respects—for instance, A prevents and cures xerophthalmia and osteomalacia, whereas B does not. Finally, the question has to be mooted whether A might not be identical with the antiscorbutic complettin C. Apart, however, from the consideration that the effects of A and C are entirely different, direct proof that the two substances are distinct has been furnished by Givens and Cohen,[754] Harden and Zilva,[805] and Mellanby.[1135] We are therefore constrained to admit that the complettin A is a distinct substance, not identical with any of the other recognised growth-promoting or life-sustaining substances. We shall now proceed to consider the properties of A, excluding reference to any properties that might be ascribed to confusion with other substances, or to impurities.

5. Properties of the Complettin A.

In 1909, Stepp[93] drew attention to the solubility of this complettin in alcohol, and the fact has been confirmed by all subsequent investigators.[396, 419, 424, 427, 526, 714, 1142, 1150] It is but slightly soluble in water,[714] and cannot be extracted from fat by water.[875] It is, however, soluble (though not very readily) in the ordinary fat-solvents acetone,[526] benzol, chloroform,[1142] and ether,[419, 427, 526, 714, 1142] but cannot be completely extracted by these menstrua. When, however, A is first extracted with alcohol, and the extract is evaporated down, the complettin can then be fully extracted from the residue with ether. This provides a good method of purification. For example, green vegetables, having been dried and pulverised, are treated with benzin or with ether to extract the fat; the complettin is then extracted with alcohol; when the alcohol has been evaporated off, the residue is extracted with ether; when the ether has been evaporated, the complettin is left in a fairly pure state. For dietetic experiments it can then be dissolved in olive oil which has been previously freed from A. (Cf. Zilva, 1150.)

Speaking generally, however, the complettin A (though specifically termed "fat-soluble") is not readily dissolved by fats, and cannot be extracted from vegetable nutrients by vegetable oils or by lard.[714, 1142]

Funk and Macallum [374] began by isolating A by the method then in vogue for the isolation of vitamin, namely by extraction with 0·5 % hydrochloric acid; but obviously all they could get in this way were specimens of A containing vitamin as impurity—this being, indeed, manifest from the other data of the investigation. Drummond [875] declares, moreover, that A is almost insoluble in hydrochloric acid. The non-identity of A with vitamins, with B and with D, and above all with C, is best shown by the reaction of the respective substances to alkalies. Whereas the other complettins all appear to be more or less sensitive to the action of alkalies, A is apparently unaffected by them. Steenbock, Boutwell, Gross, and Sell [1142] actually declare that fats containing A can be fully saponified by 6 % alcoholic solution of potash without the A being notably affected, even though the action of the alkali has been continued for several days. Drummond,[875] however, tells us that there is a certain loss of A in this process, perhaps due to oxidation—see p. 229. By shaking up the soap solution with ether and evaporating off the ether, an extremely effective residue was obtained. This could be further purified by dissolving it in a mixture of alcohol and petroleum ether (naphtha), and then adding water, shaking up, and allowing the solution to separate into layers. The A, together with the carotin, passed into the naphtha stratum, whereas the alcoholic xanthophyll solution contained no more than traces of it. This report suggests that the obtaining of A in a pure state ought to be possible, and it could be wished that with this end in view the physiologists would seek the aid of a competent chemist.

As regards thermostability, the complettin A differs greatly from the complettins hitherto considered, and also from C. Nevertheless, as Osborne and Mendel [702] and Ramsden [714] insist, the power of resisting heat is greatly influenced by the conditions under which the heat is applied, one of these conditions being the nature of the menstruum. Thus Mendel [1223] reports that A in butyric oil is less resistant

to heat than A in aggregate butter. In butter, A will resist long-continued steaming,[424, 1132] fifteen hours' heating at 95° C.,[1132] and even four hours' heating at 120° C.[1034]; but it is destroyed by longer heating at these high temperatures.[396, 427] Yet Steenbock, Boutwell, and Kent [752] found that when butter was shaken up with hot water for a long time, the A it contained was seriously injured; and they considered that the injury was due to the effect of heat. Stepp [234] reported that two days' boiling of the active lipoids, or of the aggregate food, in alcohol, or more prolonged boiling in water, destroyed the activity of the substance.

According to Delf,[806] the growth-complettin A in green cabbage resists ordinary boiling, but it is somewhat impaired by keeping the dried cabbage for from one to two hours at a temperature ranging from 100° to 120° C., and is very seriously injured by two hours' dry heating at 130° C. On the other hand, Steenbock and his collaborators [1054] inform us that the A in green cabbage is not affected by three hours' heating in the autoclave under fifteen pounds pressure.

The contradictory character of the foregoing reports is mainly explicable by the supposition that the complettin A is readily oxidisable. According to Drummond,[875] when the food containing A is heated in thin layers to 100° C., the A is destroyed within an hour, whereas several weeks' exposure to a temperature of 37° C. is requisite to effect destruction. Subsequently, Drummond and Coward [1324] gave direct confirmation of the hypothesis that the cause of the destruction must be oxidation by atmospheric oxygen. This, likewise, is the plain inference from the experiments of Hopkins,[1034] who found that four hours' heating of butter at 120° C. had no deleterious effect upon the A it contained, whereas the A was completely destroyed within the same period at this temperature when air was forced through butter all the while. In a subsequent and extensive series of experiments,[1315] Hopkins confirmed the theory that A is readily oxidisable. According to Zilva,[1325] ozone, even in the dark, speedily renders A completely inactive; and ultraviolet light will quickly destroy A in codliver oil when air or ozone is present, but has no effect when the oil is in a carbonic-acid atmosphere. The sensitiveness of A to light was pointed out in

1918 by Ramsden,[714] who did not, however, recognise the real bearing of his own observation.

We may, therefore, assume that when air is excluded, or when a nutrient is heated in compact masses, the complettin A will tolerate even prolonged heating at 120° C. under atmospheric pressure or under greater pressure. But when air has free access (either because the nutrient is heated in thin layers, or because it has been pulverised, or because it is in dilute solution, or because air is directly conducted through it), A is speedily destroyed by a high temperature. This explains why it is that when lactalbumin [898] or casein [1168] is heated at 120° for a long time in thin layers, the traces of A these substances contain are destroyed, and yet that butter can be exposed to the same conditions without appreciable loss of A.

We can also understand why the drying of vegetables, especially when the drying is effected in the customary manner at a moderate temperature,[1132, 1312] is harmless to the A they contain, and that the dried material can safely be stored in large masses with the exclusion of air; but that when the A-containing substances are preserved in the powdered state, and especially in open vessels, the complettin A is soon destroyed.[807] This explains, likewise, why butter can be preserved in bulk for years without the loss of efficiency of the A it contains, whereas butyric oil no longer contains any effective A after a year's storage.[477] Delf and Skelton [807] describe the drying of vegetables as an undesirable method of preserving them; but the foregoing considerations will show that, as far as the A content is concerned, this is true only if the dried vegetables are freely exposed to the action of the air.

6. Physiological Action of the fat-soluble Complettin A.

When there is a deficiency of A in the food, just as when there is a deficiency of B, the first effect is an arrest of growth (in young animals); then comes a rapid loss of weight, often attended with grave debility,[821, 1133] and the appetite falls off. The general debility and the lowering of the resistance to infections is even more marked when there is a lack of A than when there is a lack of B. The power

of A to enhance the resistance of the organism to microbic infection is extremely characteristic of this complettin.[876, 920, 1116] The difference between breast-fed and bottle-fed infants as regards resistance to infection is well known; Aron refers this to the high A content of the natural milk. The same authority [1112] suggests that the extreme prevalence of influenza during the last years of the war, and the malignancy of the disease at this epoch, may have been due to the general lack of A in the diet, and to the consequent weakening of the constitution.

When there is a deficiency of A in the diet, just as when there is a deficiency of B, no change can be detected in the serological constants.[917] We must therefore look to a direct loss of efficiency in the organism or its cells to account for the diminished powers of resistance. No doubt one of the effects of wartime feeding was the widely noted diminution of the haemoglobin richness of the blood; but war feeding was defective in so many respects that we are hardly justified in laying the blame upon one defect in particular. Stepp [884] certainly found that in dogs fed on an A-free diet there was a marked decline in the haemoglobin richness of the blood, although the number of the erythrocytes remained normal. Dalyell,[1055] in a Viennese child suffering from grave malnutrition, found that the provision of A in the diet was followed within two-and-a-half months by an increase in the haemoglobin richness of the blood from 38 % to 70 %.

The effects of A and B in respect of growth are of course manifest only in growing animals, and in like manner the effects upon body-weight are far more manifest in young than in adult animals—more manifest in proportion to the activity with which growth should be proceeding.[459] We find also that the effect of A deficiency in reducing resistance to infections is less marked in adults.[389] Nevertheless, A is essential to adults for the maintenance of body-weight and a good general condition.[876]

7. A in relation to Xerophthalmia and to Keratomalacia respectively.

The lowering of resistance to infection gives rise, especially in youth, to an affection of the eyes which may be

regarded as pathognomonic of A deficiency. This disease is known as xerophthalmia, which usually passes on rapidly into keratomalacia. Of all the tissues of the animal body, the cornea is perhaps the most completely removed from the direct influence of the blood stream, and it is therefore only to be expected that any important change in the bodily juices should speedily produce effects upon the cornea. The lack of A in the food gives rise to a general dryness of the skin, and it has similar effects upon the cornea. The morbid state thereby induced makes it easy for all kinds of microbes to invade the tissues of the eye, producing changes which may culminate in blindness. The occurrence of xerophthalmia in A deficiency was first noticed by Freise, Goldschmidt, and Frank [459] in rats fed on food which had been extracted with alcohol. The observation was confirmed by Bulley,[821] Hopkins,[1066] and Nelson and Lamb.[1143] The primary cause of the disease is not the infection of the cornea, but the drying of the cornea through the lack of A, which prepares the ground for microbic invasion. Bulley has repeatedly endeavoured to infect with material from cases of keratomalacia the eyes of rats fed on a diet rich in A, but has never succeeded. Or rather, among 250 young rats on an adequate diet, 5 only became affected with xerophthalmia, and in these instances there was reason to suppose that the extreme uncleanliness of the animals was the cause of the infection. On the other hand, rats fed on a diet devoid of A almost invariably became affected with xerophthalmia or keratomalacia.

Among diets especially prone to induce these diseases of the eye, the following ill-balanced diets are mentioned: potato diet [812]; nuts poor in A [1169]; cereals [682, 796];—even when supplemented with buttermilk, skim-milk, or vegetable margarine.[920] Millet and hemp seeds are said by McCollum and Simmonds [682] to prevent the onset of xerophthalmia; but according to Auer,[812] attacks may occur when millet is being given. We may assume that in millet, as in other natural foods, the quantity of A is variable; and since there is at the best but a narrow margin of sufficiency in this grain, the amount may fall below the necessary minimum. The same considerations apply to skim-milk, which will

contain very little A if the removal of the cream has been thorough. This explains the discrepancy between the observations of Bloch,[920] who found that a diet of buttermilk or skim-milk may induce keratomalacia in children, and those of Freise, Goldschmidt, and Frank,[459] according to whom buttermilk and skim-milk will cure the disease.

When the diet is rich in A (when, that is to say, it contains plenty of butter, cream, full milk, eggs,[920] or codliver oil [1057]), this affection of the eyes is rarely encountered, and then only as a result of general debility and deficient attention to cleanliness. Perhaps these exceptional instances may also be referred to a deficiency of inorganic salts in the diet, for McCollum and Simmonds [682] draw special attention to the fact that, *while A can prevent or cure the disease, it can only do so when the diet contains an ample supply of sodium and potassium.*

For the cure of xerophthalmia or keratomalacia, extracts rich in A,[1243] and natural nutrients rich in A, such as butter,[682, 920, 1055] cream, full milk, eggs,[920] and codliver oil,[920, 1055] will be found valuable; the same substances are efficacious as prophylactics.[682, 714, 812, 821, 1243, 1312]

8. A in relation to Osteomalacia.

Like the cornea, the cartilages and the osteogenic tissues are poorly supplied with blood, and they too therefore are especially apt to suffer when A is lacking in the diet.[1055] In experiments on animals, changes in the bones are less conspicuous than changes in the cornea, so that reports upon bone disorders are rare. According to the experiments made by Mellanby [1055] in the years 1918 and 1919, young dogs supplied with a diet poor in A but otherwise adequate become "rickety"; but the author's descriptions suggest rather the onset of a rachitis tarda, which may be regarded as identical with osteomalacia. According to Barnes and Hume,[969] the chief characteristic of this disease is a rarefaction of the osteoid tissue, which in the neighbourhood of the epiphyses may be reduced to the thinness of paper; the spongy tissue may more or less completely disappear, but the chemical composition of the bone is not affected. In true rickets, on the other hand, there is softening of the

bone tissue with a predominant loss of calcium salts, so that the bone-ash in cases of rickets exhibits an abnormal preponderance of magnesium salts.

Weiser,[347] feeding pigs on an exclusive diet of maize, noted the onset of "ricket-like" diseases of the bones, and he considered that rickets was actually present. It is true that in the experimental animals there could be detected in the canial bones, the ribs, and the vertebrae, a moderate increase in the proportion of magnesium, and that this observation might be taken as confirming the rickets theory But in rickets the most pronounced changes occur in the bones of the extremities, and in the experimental animals these bones contained a normal percentage of magnesium—or in some instances even a little less than normal. We can, therefore, confidently infer that the disease was not rickets, but osteomalacia.

Scheunert, Schattke, and Lötzsch [181] reported the onset of a similar disease in horses fed on hay of abnormal composition. They considered that the unusually low proportion of lime and phosphorus in the hay was the pathogenic factor, and we know that in abnormal vegetable products the A content may be too low. Scheunert [1088] has recently reported another case in which osteomalacia occurred in horses fed for ten years in the same stable. In this instance, the fodder was normal as regards richness in inorganic salts, and the only obvious defect in the diet was that the drinking water was very poor in calcium. Scheunert thinks that the illness was due to an infection of the stables and the drinking water with a diplococcus which gave rise to digestive disorders in the horses, resulting in a general modification of the intestinal flora and in the abundant formation of lactic acid in the intestine. Both these instances are extremely interesting in more ways than one, and I shall return to their consideration shortly.

During the later years of the war, osteomalacia and other forms of osteopathy were frequent, and in the large towns sometimes assumed epidemic proportions. This tends to confirm the opinion that the complettin A is essential to the normal metabolism of the bones. It has been widely believed that the cause of these troubles must have been

some lack in the diet, especially a lack of calcium and phosphorus,[933, 965, 1031, 1078, 1290, 1306] but other authorities have spoken of a "lack of vitamin."[933, 1078] The latter assumption is confirmed by the following considerations. First of all, the bone disorders were frequently associated with signs of disorder of the endocrine glands, such as amenorrhoea in adult women and a failure of menstruation to begin in girls at the age of puberty (cf. Blencke[1078]), and by nervous symptoms, such as tetany and other spasmodic troubles.[1078, 1165] In the second place, the diseases were curable by a diet rich in A, and especially by the administration of codliver oil [933, 1078] or of phosphorated codliver oil.[933, 965, 1306]

9. A in relation to Rickets.

Obviously, the onset of such bone diseases when the diet is lacking in A, in conjunction with the specific antirachitic effect of codliver oil (a substance rich in A), has given rise to the view that rickets is caused by a deficiency of A in the food. Osborne and Mendel[350] (see also Aron[781]), who were the first to discover that codliver oil contains A, promptly thereon gave expression to the opinion that the therapeutic value of codliver oil in rachitic disorders must be due to the A it contained. The suggestion received additional support when it was found that osteomalacia was prone to arise when the diet was deficient in A. But the hypothesis has never secured unconditional acceptance among experts. Röhmann[472] considers that the main cause of rickets is, either a lack of calcium in the food, or inadequate absorption of calcium by the intestine, "with the possible collaboration of" a disturbance of the hormonic secretions that control the formation of bone. McCollum, Simmonds, and Parsons,[691] and also Dalyell,[1238] while admitting that the lack of A has some causative influence in the production of rickets, nevertheless regard this influence as subsidiary, and stress the importance of other errors of nutrition (notably, the lack of B, C, calcium salts, and phosphorus), together with the significance of the general conditions of life and that of the care of the body. As regards the diseases of bone that occurred in Mellanby's dogs,[1055] it is evidence against the presumption that they were rachitic, that a cure

ensued when butter or full milk was added to the animals' diet—for in children suffering from rickets, the administration of full milk in the absence of codliver oil is apt to make matters worse.

At first, misunderstanding arose in these investigations through the reiterated confusion between A and B in plants.[1135] But the further research went, the more was doubt cast upon the accuracy of such views. In 1920 Mendel himself said that he considered it dubious whether A really had anything to do with the causation or cure of rickets [1223]; and Mackay, an authority on the diseases of childhood, has expressed the same view.[1328] It is a familiar and indisputable fact that codliver oil has a specific effect both in the prevention and in the cure of rickets.[1035, 1057, 1369, etc.] But it is probable that the value of codliver oil may depend upon factors of an unknown nature, factors which have no connection with the A content of the oil. Bordering on the absurd is a statement by Hamshire and Hawker [914] to the effect that rickets can be cured by a proprietary preparation "rich in vitamins," known as "University Cream," and consisting of beef suet, olive oil or earth-nut oil, syrup, benzoic acid, and decoction of Irish moss.

In 1920, the British Medical Association held "A Discussion on the present Position of Vitamins in clinical Medicine," [1055] which served to clear up the problem a good deal. Whilst Hopkins expressed the opinion that the fat-soluble factor, though not (by its absence) the sole cause of rickets, was certainly an important etiological factor, and whilst Hess looked upon Mellanby's discovery as very important, Hess himself insisted that a number of other factors both organic and inorganic must play a part in the pathogenesis of this disease. Many mistakes had arisen from confounding slight cases of scurvy and other affections with incipient rickets. Still insisted upon the indispensability of the fat-soluble complettin, but reported that milk which had been sterilised by the addition of hydrogen peroxide and warming —being thereby freed from A—induced in children not rickets but scurvy. Mann likewise regarded rickets as the outcome of a complex of causes, the chief of which was a dearth of fat in the diet. (Why then do infants fed on full

milk become rickety?) Pritchard spoke of numerous factors as contributing to the causation of rickets: defect or excess of one or other constituent of the diet; lack of fresh air or bodily exercise; chronic infections, especially of the gastro-intestinal tract. All of these combined to increase the need of the organism for calcium, so that the supply to the growing cartilages was insufficient.

To anyone thoroughly well acquainted with the conditions under which rickets arises, these views are obviously full of contradictions. First of all it has repeatedly been shown that human nurselings often become affected with rickets even though their food contains plenty of A. Again, it has long been known that in cases of incipient rickets, the presence of a superabundance of calcium in the food does no good unless codliver oil be simultaneously administered. Finally, even though the diet is persistently poor in calcium, codliver oil can cure rickets, although the cure is certainly expedited by the simultaneous administration of calcium salts, and especially of soluble tricalcium phosphate. All these circumstances have been expounded in masterly fashion in the writings of Herbst and of Schloss. In especial, the last-named author, whose premature death during the war is profoundly to be regretted, has given an extraordinarily clear and vivid picture of the disease. He describes rickets as a constitutional affection of the osteogenic tissue, whereby not merely is the growth of the bones hindered, but, further, the deposit of calcium salts in the osteogenic tissue is interfered with by a reduction in the affinity of this tissue for calcium salts. The specific effect of codliver oil consists in a stimulation of the affinity until it attains a normal or even a supernormal level, so that the osteogenic tissue is rendered competent to assimilate with the utmost energy the available calcium, even though this be presented in very small quantities.

These epoch-making writings of Herbst and Schloss, which for the most part appeared during the war, have not received sufficient attention from British medical authorities, who are rather inclined towards conservatism. But while the failure of the British in this respect is excusable, I find it impossible to excuse the German faculty for its neglect

of these remarkable contributions of Schloss and Herbst. It seems to me characteristic of the mentality of my countrymen that, while uncritically accepting foreign opinions, they should ignore the best productions of German science. It would seem as if there were justice in the contention that there is an ebb in German science, and that the leadership has now passed to the Americans. A tragical outcome of the war, and perhaps for the German nation the worst of all its outcomes!

To summarise the present position of our knowledge, it is certain that some sort of inadequacy in the diet must be a predisposing cause of rickets and a contributory factor in maintaining the disease. On the other hand, it is proved that neither a liberal supply of A, nor a superabundance of calcium salts, nor both combined, can avail prophylactically or therapeutically unless codliver oil (which must not be too highly refined) be used as the vehicle for A. It would seem, therefore, that the richness of codliver oil in A is a mere accessory to the antirachitic action of this specific. The effect of codliver oil in rickets may be fortified by the richness of the oil in A, but must have other essential causes. In fine, the only certain prophylactic is breast-feeding by a mother able to supply good milk.

10. A in relation to Pellagra.

No less uncritical than the contention that a lack of A in the diet is the main cause of rickets, is the assumption of McCollum and his collaborators [691] that A deficiency is a cause of pellagra. In Chapter Nine we shall show that this assumption is untenable.

11. A in relation to malnutritional Oedema.

Equally unsound is the contention of Hopkins that A deficiency is important as an etiological factor in the production of malnutritional oedema. Chick [1237] is also inclined to regard a lack of A in the diet as one of the causes of malnutritional oedema; and according to McCarrison [1240] the normal action of A is to keep down the adrenalin content. When the fat-soluble factor is deficient in the diet, the adrenals hypertrophy, and there ensues an excessive produc-

tion of adrenalin, leading to oedema. We discussed this theory on p. 145, and showed there that it involved an inverted view of the facts, and that McCarrison had withdrawn his contention.[1055] Nevertheless, it is possible that a lack of A in the diet may be a contributory cause of malnutritional oedema. To this matter we shall return.

12. Action upon the endocrine Glands.

Though it seems probable that as regards the osteopathies, as regards the causation of osteomalacia and rickets, the importance of the fat-soluble complettin has been considerably overestimated, its influence upon body-weight and growth has been definitely proved. This influence is fully considered in Chapter Five, and all that is now requisite is to present a few important facts which are essential to the better understanding of the effects of A in the organism. We have seen that in growing animals and human beings, when there is a deficiency of A in the diet an arrest of growth ensues; then comes a decline in body-weight, gradual at first, and subsequently rapid; there is profound debility, which often proves fatal unless a speedier death should have resulted from some intercurrent disease due to the lessened resistance to infection and other noxious influences. A conspicuous effect of A deficiency is a general atrophy of the endocrine glands, the only exception being the adrenals, which hypertrophy just as they do when there is a deficiency of Funk's vitamin.[876] The researches of Verzár and Bögel [1270] have shown that, like B and D, A is absolutely non-toxic alike in cold-blooded animals and in mammals, and that in dogs affected with diabetes from operations on the pancreas neither the size of the pupils nor the excretion of sugar is affected by their administration. But A differs from B and D in that it has no effect upon the secretion of the glands. Consequently the atrophy of the endocrine glands in A deficiency must be due to an interference with the normal nutrition of these organs. The reduction in their secretion is merely an indirect consequence of the atrophy.

Verzár and Bögel report, in addition, the interesting fact that A is a vasodilator, that it has an action antagonistic to that of adrenalin. All the more striking is it, then, that

the adrenals should undergo hypertrophy when there is a lack of A, for there would not seem to be any direct occasion for a surplus production of adrenalin. The lack of A must enhance the effect of the adrenalin, and the hypertrophy of the adrenals must be regarded as a direct consequence of the A deficiency—but the way in which this effect is produced is still to seek.

According to Drummond, the deposit of fat occurs in animals quite normally when A is lacking, and the milk of lactating animals remains perfectly normal in respect of fat content [876]; but a sufficiency of milk for the growth and the normal development of the offspring can only be secreted by the mother when her food contains an adequate supply of A. The lacteal glands cannot themselves manufacture A; but, just as they are able to call upon the maternal organism, even at the cost of its own health, to supply all the other necessary constituents of normal milk, so are they in a position, when there is a lack of A in the diet, to commandeer whatever quantities of A may be circulating in the maternal blood and to secrete them in the milk. According to McCollum and Simmonds,[1026] only when the lack of A in the maternal diet has been long continued does there arise a deficiency of A in the milk, and the effects of this are promptly manifested in the sucklings by an arrest of growth, by debility, and by a proneness to xerophthalmia.

The facts just recorded indicate clearly that the fat-soluble complettin A cannot be synthetised in the animal body, and that the animal organism's need for this substance can be satisfied in no other way than by its provision ready-made in the food.[234, 561, 1026, 1170] The ultimate source of the fat-soluble complettin is, therefore, the vegetable kingdom. The main supply would appear to be derived from the green and growing parts of plants, but in exceptional instances it is found in the stored-up fat.

The various yeasts and microorganisms are able to synthetise A for their own needs, and are therefore independent of supplies from without. Very interesting, therefore, is the statement of Willaman [1043] (if correct), that certain fungi, and notably Sclerotinia cinerea, appear to need a supply of A, being otherwise incompetent to form spores. We must

assume that, just as in the case of animals (which are all parasitic upon the plant world), the parasitic mode of life of these fungi has led to a degeneration of the parasites in this respect, so that they are no longer competent to satisfy their need for A by independent production, and are compelled to draw upon the stores of the host.

In conclusion let me emphasise the fact that the effect of A is of course subject to the law of the minimum to this extent, that when some other essential constituent of the diet is wholly lacking or is supplied in inadequate quantities, even the most liberal provision of A can have no effect. As regards proteins, fats, and carbohydrates, and as regards the other complettins, the fact will be obvious to everyone. But people are so apt to overlook the importance of inorganic salts that I find it necessary to insist once more that an adequate supply of these substances (adequate both qualitatively and quantitatively) is an indispensable prerequisite to the effective action of A. We have already seen [682] that on a cereal diet a supplement of A remains without effect unless the inorganic content of the diet be likewise supplemented by the addition of sodium and calcium until there is an excess of bases. In like manner, McCollum and his collaborators have shown [1026] that, even when there is plenty of A in the diet, the maternal organism cannot secrete sufficient milk, and therefore that the progeny cannot thrive, unless the mother's food likewise contain an adequate amount of inorganic salts in due proportions. Aulde [1259] has also shown that a lack of calcium, when complettins are supplied, induces the same changes in the glands as those seen when the diet contains plenty of calcium but is deficient in complettins. Similarly, although there be abundant A in the diet, if calcium be deficient there will arise affections of the eye such as are witnessed when A is deficient; and in cases of xerophthalmia, the administration of calcium in addition to A will cure more quickly than will the administration of A alone. The only possible interpretation of these facts is that the complettins cannot do their work in the absence of the necessary inorganic salts.

CHAPTER SEVEN

THE ANTISCORBUTIC COMPLETTIN C

1. Historical.

Although the nature of scurvy was not elucidated until during the last decade, this disease is one of the oldest scourges affecting mankind in northern latitudes. An examination of skeletons dating from neolithic times, from the bronze age, and from the iron age, has shown that in Sweden during those times scurvy must have been devastating in its prevalence, whereas rickets seems to have been almost unknown. During the long winters of those northern regions, when smoked or dried meat and fish constituted the staple diet, it was inevitable that scurvy should be prevalent. At the present day, the Eskimos of North America live under conditions similar to those which prevailed in Scandinavia during the stone age—at any rate, during the paleolithic era, the greater part of Sweden was covered by an ice-sheet. Now, in summer the Eskimos, who live almost exclusively on flesh and fat, often suffer from a mild form of the haemorrhagic diathesis, being affected with bleeding from the gums, nosebleed, haemorrhages from the other mucous membranes, and severe extravasations of blood in the subcutaneous tissues upon comparatively slight provocation, while in winter, under the combined influence of famine and unsuitable diet, typical scurvy is apt to arise, sometimes carrying off entire tribes. Among the indigens of North-Western Asia, who are at an even lower level of culture than the Eskimos, and among the Ainos of Northern Japan, similar conditions prevail. The rise of large urban communities in Northern and Central Europe, populations hemmed in by the walls and moats of the fortifications, gave occasion

for long-continued epidemics of scurvy. The town-dwellers were dependent for their food-supply upon the peasants of the immediate neighbourhood; and when there was any arrest of the provision from this source, scurvy promptly made its appearance in the cities. This was the rule as late as the beginning of the nineteenth century. An examination of the death registers of the old cities shows that scurvy took its place beside consumption and apoplexy as one of the most common causes of death.

When sea voyages grew longer, so that ships were months without communication with the land, scurvy became a frequent and dreaded guest on board. The whalers, in especial, who sometimes spent years in the far north under the most unfavourable conditions, working very hard on an unsuitable diet, suffered greatly from the disease. So did the men of the navies, who were closely herded together, and were fed almost exclusively upon badly preserved food. It was natural, therefore, that upon ships the specific value of the various sorts of lime and lemon as preventives of scurvy should first have become known; and as early as the sixteenth century, the antiscorbutic effect of fresh vegetables was familiar. But it was not until the year 1796 that the provision of lemons as a means for the prevention of scurvy was made compulsory in the British navy.

We see, then, that it was no chance matter that the impulse to the scientific study of this disease should have originated in the north, and that the pioneer investigations should have been made in a land whose population has for thousands of years furnished so large a proportion of seafaring men. In the year 1905, the Swedish physician Ekelöf [47] expressed the opinion that the disastrous effect of preserved nutrients must depend upon the generation of autolytic poisons within them. A little later, a similar idea was promulgated in Germany by M. Schubert.[51] Shortly before this, writing in the Swedish medical journal "Hygiea," the Norwegian Schmidt-Nielsen [50] had amended the theory with the suggestion that what happened during preservation was not the formation of toxins, but the destruction of important substances—enzymes, perhaps, or antibodies such as were then becoming known in connection with the theory

of immunity. Within the next year or two came the publication by two Norwegians of the most important studies incorporating the results of modern research into the nature of scurvy. In an extended series of experimental investigations, Holst and Frölich have attempted, with the aid of modern physiological and chemical methods, to throw light upon the etiology of scurvy.[62, 63, 64, 65, 101, 171, 186, 204, etc.]

First they were able to show that bread, cereals, or dried potatoes, gave rise to scurvy in guineapigs; so did dried cabbage, dried carrots, and dried dandelion. On the other hand, fresh fruits and vegetables, such as apples, potatoes, cabbage, carrots, dandelion, and lemon juice, can not only cure scurvy, but when added to a scorbutogenic diet can prevent the onset of the disease. Peas, lentils, and almonds, and also maize, give rise to scurvy in guineapigs. When nutrients which, as an exclusive diet, induce scurvy are given in conjunction, the disease still arises, and this shows that we are not concerned here with a deficiency disease resembling that which occurs when an inadequate protein is given, seeing that several inadequate proteins respectively derived from different classes of foodstuffs can compensate one another's deficiencies.[102, 187, 203] The addition of milk to the diet will prevent the onset of scurvy; but this prophylactic power is more or less completely lost if the milk be boiled, condensed, or dried. In like manner, the prolonged boiling of such nutrients as cabbage, carrots, or dandelion, greatly impairs their antiscorbutic value.

The two Norwegian scientists inferred from their studies that quite a number of natural nutrients must contain an antiscorbutic ingredient. There are other nutrients in which this substance is present in small quantities only, or from which it is entirely absent; and when such substances form the staple diet, scurvy arises. The protective principle is thermolabile, and is rendered inactive or destroyed by prolonged boiling or by drying.

Another Norwegian, V. Fürst,[102, 187, 203, etc.] confirmed and expanded these conclusions in a long series of investigations. Notably, as early as 1910, Fürst made the important discovery that oats, peas, and lentils, which in the ordinary condition are scorbutogenic for guineapigs, become during

germination so rich in the antiscorbutic complettin that their addition to a scorbutogenic diet can cure scurvy; and that as exclusive diet these germinated grains or pulses are not scorbutogenic. He found, further, that in the germinated seeds, likewise, the efficacy of the antiscorbutic complettin was gravely impaired or completely destroyed by drying. Like Holst and Frölich, Fürst drew the inference that scurvy must depend upon the absence of a natural prophylactic from the diet. Since this substance is present in milk, which is a nutrient rich in vitamin, and since vitamin is rather sensitive to heat, Funk assumed that scurvy must be akin to beriberi.[205] Numerous subsequent investigations, conducted by various authorities, have shown that the occurrence of scurvy must actually be due to the absence of some protective principle. (Cf. in especial, [391], [714], [1066].)

Fürst [187], [203] had been able to exclude acidosis and infection as possible causes of scurvy. McCollum and Pitz, however, now came forward with a new theory, according to which scurvy was indirectly, though not directly, due to micro-organisms. They held that the causation of the disease did not depend upon the lack of an accessory food factor, but upon prolonged retention of the faeces in the bowel, putrefactive processes, and consequent toxaemia.[651], [652] Pitz [693] quotes an experiment by Lusk, who found that whole grain did not bring about scurvy in guineapigs; but McCollum found that the addition of milk to a diet of whole grain induced constipation, and that the putrefactive processes which then ensued in the intestine gave rise to scurvy. Figueira,[1046] experimenting on guineapigs and dogs, came to the same conclusion.

In support of this hypothesis, stress is laid on the assertion that laxatives are said to prevent the onset of scurvy.[651], [652], [693] The same effect is supposed to be secured by a modification of the intestinal flora, leading to a replacement of putrefactive processes by innocent fermentations; in this way considerable doses of lactose are said to prevent and cure scurvy.[693] Pitz,[786] however, makes a reservation to the effect that although laxatives and lactose can retard the outbreak of scurvy for as long as twenty weeks, they do not furnish complete protection.

Other authorities have been unable to confirm these data. Moreover, according to Harden and Zilva, large doses of the alkaline citrates are ineffective,[794] although they destroy the organisms of putrefaction and have a marked laxative effect; and according to the same investigators, the free administration of sugar, which has a similar action, is valueless.[795] According to Hess and Unger,[750] laxative oils are of no use as preventives of scurvy. Hart, Steenbock, and Smith[901] were unable to prevent the onset of scurvy by modifying the intestinal flora through the administration of chemically pure lactose, or such laxatives as mineral oils or phenolphthalein. Mouriquand and Michel [1023] likewise declare that laxatives are useless for the prevention and cure of scurvy. The same authorities found that in scorbutic guineapigs the intestine was often practically empty, and they concluded therefore that stagnation of the faeces and intestinal putrefaction could not be regarded as the causes of scurvy. On the other hand, Karr and Lewis [638] have shown that in scorbutic guineapigs, even when constipation occurs, there is no increase in microbial activity within the intestine. Cohen and Mendel [749] consider that retention of the faeces has no etiological relationship to scurvy, although naturally constipation, like any other complication, can aggravate the symptoms of the primary disease. Röhmann [472] would not admit the existence of an antiscorbutic accessory food factor, and referred the origination of scurvy to protein insufficiency. But this view proved untenable when it had been shown that certain vegetable extracts which were absolutely free from nitrogen were competent to cure or prevent scurvy.

It is remarkable to find that McCollum, collaborating with Simmonds and Parsons,[691] has insisted that in the production of scurvy other causes must be operative in addition to the lack of A or B, and that Funk's vitamin has nothing to do with this disease. Aron, too, insists that the curative effect of fresh fruits and vegetables in infantile scurvy depends upon the presence of water-soluble extractives.[781] Willcox [1025] came to the same conclusion from his study of scurvy among the British troops in Mesopotamia during the recent war. Bierich,[954] again, regards scurvy as dependent upon a denaturation of the food whereby it is rendered qualitatively inade-

quate. Quite isolated stands the report of Funk [527] to the effect that antiscorbutics are valueless in guineapigs. The animals were being fed on oats, and Funk's experience of the valuelessness of antiscorbutics is in such flat contradiction with the experience of all other investigators that we are forced to assume the presence of some grave error of diet as a contributory factor—perhaps a lack of calcium. It is, of course, hard to believe that so noted and experienced an investigator can have made such a mistake, but this is the impression left upon my mind by the secondhand reference to which I have alone had access.

However, all the more recent researches point to the conclusion that the cause of scurvy is a lack of complettin in the diet, and Drummond [874] *has christened the complettin specifically active in connexion with scurvy "water-soluble C."*

2. Scurvy Epidemics during recent Years.

Prior to 1914, people had come to regard scurvy as a disease belonging to obsolete stages of social evolution, as one of which civilisation had made an end. But the war of 1914 to 1918, and the subsequent years of alleged peace, have furnished plenty of opportunities for the study of scurvy on the European continent, and notably in the armies. A foretaste was provided in the last Balkan war, when scurvy was rife in the Bulgarian army, although preserved vegetables had been supplied as prophylactics. I have repeatedly had occasion to insist that these preserved vegetables were probably the cause of the disease. For the water-soluble antiscorbutic complettin, just like the excess of bases, is removed by the "bleaching" process which (despite all that has been said against it by scientific authorities) is still in vogue for the factory preparation of these preserves. Thus the vegetables which were specially intended to prevent scurvy, must have favoured the incidence of the disease.

Willcox [1025] has published a detailed account of the epidemic of scurvy among the British troops in Mesopotamia. In order to prevent beriberi among the Indian soldiers, instead of rice they were given "ata," a barley flour containing a good deal of bran and an abundance of vitamin, but poor in C. The men had no fresh meat, no vegetables, and no fruit,

and the result of this diet was a severe outbreak of scurvy. The onset of the disease was favoured by the circumstance that the men had already been weakened by the long sea voyage, were under-nourished, anaemic, and suffering (many of them) from dental caries when they arrived at the theatre of war. Doubtless, too, their powers of resistance were weakened by the terrible climate, the uncertainty of their fate, and the home-sickness which must have been accentuated by the contrast between the Mesopotamian deserts and their native land. Willcox considers that the main factors of the cure were the supply of fresh vegetables and fruit and fresh meat; and he states that a salad made with malt vinegar of raw, thinly sliced potatoes and raw onions was especially efficacious. He insists that the lack of complettin in the diet must have been the main cause of the disease.

It is well known that, during the war, scurvy celebrated positive orgies in Northern Russia, and the building of the Murmansk railway will be ever memorable in this respect. A British doctor, J. D. Comrie,[1118] has given a detailed description of the affair, and his account may be summarised as follows. Among the Russian troops, scurvy was comparatively infrequent, owing to the abundant supply of potatoes, pickled cabbage, fresh meat, and fresh fish; and among the British troops which, in accordance with the suggestions of Chick and Hume, were given germinated beans or peas as a prophylactic, the disease was exceedingly rare. It was, however, terribly severe among the prisoners of war, who were put upon extremely strenuous work and who lived under the most unfavourable and insanitary conditions. From the descriptions of German prisoners of war who escaped from Murmansk, we know that the Russians had no time or sympathy to waste on prisoners who were affected with scurvy. Anyone who became unable to work was left to perish like a dog, unless a Russian soldier might be compassionate enough to put him out of his misery with a blow from an axe or with a bayonet thrust. The six hundred cases Comrie describes as having been treated in the hospitals of Murmansk and Archangelsk were no doubt drawn from among the prisoners of war who were lucky enough to be working in or near these towns. The diet is said to have been fairly

varied, consisting of flour or biscuit, rice, oats, peas or beans, frozen meat or tinned meat, salted herrings, bacon, salt pork, tea, sugar, salt, and preserved lime juice—the last, we may presume, only in the towns. Comrie tells us that the rations were meagre, and that the diet was extremely poor in carbohydrates; and we know from other sources that in actuality the diet was less varied than on paper, and that the quality of the nutrients left much to be desired. But even if these foodstuffs had been unimpeachable in quality, even if they had been supplied according to schedule and in abundance, they would still have induced scurvy, for the diet named contains very little C, and the preserved lime juice of commerce is of course quite inactive. In Murmansk, therefore, the lack of C must have been the main cause of scurvy.

Outbreaks of the disease, however, were not confined to these remote corners where the supply of food satisfactory both as to quality and quantity was a difficult matter; scurvy made itself known in even Western Europe. The British had experience of it from time to time when the supply of potatoes was tending to run short.

Wiltshire [1303] reports upon an epidemic of scurvy in 1917 among the Serbian soldiers on the Salonica front. In this instance, the scorbutogenic diet consisted of bread and meat, the latter being mainly tinned meat or frozen meat cooked by boiling. Small quantities of the lime juice of commerce did not prevent the occurrence of scurvy. Wiltshire mentions cases in which scurvy occurred although "an abundance" of boiled potatoes, onions, and spinach had been eaten; here we may suppose, either that the boiling had been unduly prolonged, or else that the water of the first boiling had been thrown away. Special researches made by this investigator showed that germinated beans, which were used after a time both prophylactically and therapeutically, were far more effective than fresh lemon juice. Even severe cases, which resisted treatment with lemon juice, were speedily cured by germinated beans. Here, then, manifestly a lack of C in the diet was the decisive etiological factor.

Chick,[1237] who studied the illness among children in England and in Vienna, found that the main defect of wartime feeding was everywhere a poverty in C, to which a lack of A, B, and

inorganic salts, was often superadded. Somewhat earlier, Frank [1005] had drawn attention to the frequent occurrence of infantile scurvy among artificially fed infants in the Viennese Institute for Mothers and Nurselings. Chick and Dalyell [1055, 1238, 1278] describing their Viennese experiences, insist upon the poverty in the children's food in respect of C ; and they say that the trouble was accentuated by the fact that, on the one hand, the institutional diet (containing an abundance of calories) induced rapid growth among the children, and, on the other hand, there were grave errors in the preparation of the food. Thus, in general, the period of boiling was excessive ; and, after boiling, the food was usually kept warm for a long time, whereby the complettin content was yet further reduced. Most disastrous of all is the practice common in South Germany of preparing vegetables by first boiling them and pouring away the water in which they have been boiled, and then masking the insipidity of the flavour by adding a sauce made of charred flour and fat ! When, at the sun-bath station of the Viennese University Clinic it became necessary during the winter to restrict for eight weeks the supply of fresh vegetables, scurvy appeared with positively explosive violence.

I must refer in passing to an exceptional instance [1114] in which scurvy appeared in a four-year-old child nourished almost exclusively upon soup, coffee, and boiled milk—with the remark that such cases are, in truth, far less exceptional than might be supposed. In Germany, when they are mild, they are usually confounded with rickets ; but at least two instances of epidemic scurvy in institutions were recorded in this country during the war. I shall presently have to refer to the outbreak of scurvy in the Frederick the Great Orphanage at Rummelsburg near Berlin, described by Erich Müller.[1268] The other epidemic was reported by H. Vogt,[1042] who in 1919 had nine cases of infantile scurvy under observation in the Altstadt Hospital in Magdeburg. The terrible rise of prices in Germany is, at the time of writing, the cause of the frequent occurrence of scurvy, for many people are living almost exclusively on bread.[1555, 1556]

Finally, during the last years of the war, the Swedish newspapers contained numerous reports of epidemics of scurvy

in Northern Sweden. The diet in this area consisted mainly of very coarse, bad bread, with a small quantity of potatoes and salt bacon, the beverage being a coffee substitute without sugar or milk.

3. Occurrence of the antiscorbutic water-soluble C.

a. Occurrence.

The complettin C is found in special abundance in fresh vegetables [751, 800, 1066] and fruits.[1066] The various fruits of the genus citrus (lemons, limes, oranges, etc.) have long been renowned as antiscorbutics. The richness of these fruits in C appears to vary directly with their sweetness. McClendon [1129] has even maintained that natural nutrients in general are richer in C in proportion to their sweetness. But this assertion must be accepted with reserve; and certainly honey,[296] the sweetest of all natural products, contains no C. The lemon in common use, and its juice, though when fresh both are very active,[65, 1066] is less rich in C than the lime,[1177] while the orange and its sweet juice are richest.[491, 577, 1066] The inner layers of orange peel are likewise rich in C, and as a supplement to an otherwise scorbutogenic diet can act as a valuable prophylactic and curative agent even after months of drying.[751] The juices of other fruits are curative in scurvy [411, 1066]; some of them, like grape juice, are effective prophylactics.[1066] Apples do not contain much C, but are curative; cucumbers,[1066] tomatoes,[838, 1066] and bananas,[969] are both prophylactic and curative. According to Weill and Mouriquand,[756] vegetables and fruits contain more C in proportion as they are greener; when they ripen, their richness diminishes. In conformity with this statement, we find that ripe hay, according to Hess and Unger,[750] contains very little C, and straw even less.

White cabbage in small quantities as supplement to an otherwise scorbutogenic diet is both prophylactic [171, 186, 577, 754, 1053] and curative,[65, 105, 806] but is less rich in C than spinach.[831] Fresh green cabbage is as rich as oranges in the antiscorbutic complettin.[1115] I have already mentioned that dandelion can prevent the onset of scurvy [186]; and other

green leaves, such as the blades of cereals,[1199] and timothy grass,[831] are rich in the complettin C. Even richer than orange juice are spinach,[831] lucerne,[831, 1053] and, above all, clover.[831, 1053] Onions are said to be very rich in C, and in the raw state (like potatoes) are reported to be most valuable for the cure of scurvy.[1025, 1066] Even when boiled, potatoes contain enough C to prevent scurvy.[56, 105] Beetroots[918] and carrots[105, 918] can cure scurvy, and can prevent it[105]; and both the alcoholic[391] and the aqueous extract of carrots[1066] possess this power in a high degree. Among root crops, ripe turnips are especially rich in complettin C[918, 1057]—almost as rich as oranges. But the complettin C in turnips seems to be less affected by storage and less thermolabile than the same complettin in oranges.[1115]

According to British physicians,[1066] fresh meat and raw meat juice were found extremely effective against scurvy. If this be so, either the amount of C in meat must be very variable, or else there must have been given in addition to flesh-meat some such organ as the liver (which is especially rich in C)—for, according to Dutcher, Pierson, and Biester,[1184] muscular tissue contains very little C. But the British doctors gave, in addition to the meat, not only milk, and oranges, lemons, etc., but also the before-mentioned salad made of raw potatoes and onions with malt vinegar. We need not, therefore, attach much importance to the supposed effect of the meat. On the other hand, we know that polar explorers (Amundsen, for instance, in the South Polar region), though their diet has consisted mainly of biscuit, chocolate, and meat dried in the cold, or tinned meat, have been able by the occasional consumption of fresh seal meat to keep the dreaded scurvy at bay. We must either assume, with Dutcher, that the flesh of sea mammals contains more C than that of land mammals; or else we must suppose that the polar explorers ate such large amounts of the fresh seal meat that they obtained enough complettin despite the small proportion of it in muscular tissue.

It is not surprising that green, unripe beans should be found to be rich in C,[918] and to be curative in scurvy, for in this stage of development they must be regarded rather as vegetative than as reproductive organs; but very remarkable

indeed is the report of Hess,[491] that ripe cotton seeds can prevent scurvy. For we know that wheat,[831] barley,[749, 885] oats,[105, 527, 577, 749, 750, 841, 885] and soy beans,[749, 831] cereals in general,[65, 816, 693] seeds in general,[187, 203] bread,[64, 65, 186, 1025] and the brans of the cereals,[885, 969] are so poor in C that they have always proved inadequate. We have learned that hay contains too little C. Its poorness in this respect may either be due to storage; or, more probably, to the ripening process, for Rossi [741] states that dried green grass, as a supplement to an oats diet, can prevent scurvy in guineapigs.

Opinions differ concerning the value of cow's milk as an antiscorbutic. According to Frölich,[107] Hopkins,[267] Barnes and Hume,[969] and Willcox,[1066] fairly small quantities of milk suffice to ward off scurvy; but according to Cohen and Mendel,[749] Osborne and Mendel,[737, 831, 1131] Chick, Hume, and Skelton,[689] and Wollman,[892] fresh milk contains but little C, its richness being stated by Chick, Hume, and Skelton to be less than one-hundredth of that of orange juice. Heim [533] witnessed the onset of scurvy in adult guineapigs on an exclusive milk diet. Pitz [693] feeding guineapigs on oats, was not able to prevent the outbreak of scurvy by supplementing the oats with a fairly abundant ration of milk.

b. Natural Variations in C Content.

Apart from the varying resistance of the experimental animals, the contradictions in the before-mentioned reports are readily explained by the consideration that the C content of the different fodders and other nutrients may vary considerably at different times. In such substances as hay, which is among the nutrients that stand on the borderline between adequacy and inadequacy, the variations may make the nutrient inadequate at one time whereas at another time it may contain a fairly liberal supply of C. More especially does this consideration apply to milk. The animal organism is just as incompetent to synthetise the antiscorbutic complettin as to manufacture the other complettins for itself; it is entirely dependent upon the supply of C in the food.[1026, 1299] According as the food contains more C or less, the animal organism will possess a larger or a smaller amount of C. It is true that the mammary glands have the power in the case

of C that they have in the case of the other three complettins and in the case of the different proteins and inorganic salts. When C is sparsely supplied in the food, the quantities that are circulating in the maternal organism are commandeered for the milk. But such a process has inexorable limits, and we have seen that in the case of the growth-complettin B, and still more in that of the fat-soluble growth-complettin, when they are persistently lacking in the diet of a lactating animal, the milk, though otherwise normal in composition, may be deficient in these complettins. Manifestly the complettins are of such vital importance to the maternal organism, that the commandeering process by the mammary glands cannot go beyond a certain point. As regards inorganic salts, the self-sacrifice of the maternal organism may proceed to such a pitch that grave diseases (osteoporosis, for instance) may ensue. In the case of the three main classes of nutrients —proteins, fats, and carbohydrates—the maternal self-abnegation may result in severe signs of malnutrition appearing in the mother at a time when the milk, though certainly restricted in quantity, still contains the normal proportions of the three main nutrients. But as regards the complettins, matters do not go so far as this. When studying beriberi we learned that sucklings may become affected with beriberi at a time when the mother still appears healthy, for her milk is deficient in vitamin. The secretion of milk containing no growth-complettin would be an absurdity, and when the supply of this complettin runs short, the quantity of the secretion is reduced; but the proportion of A in the milk may fall off to such an extent that growth is inadequate and the offspring become rachitic or are affected with xerophthalmia. It would seem that the C content of the milk can be even more readily reduced. To express the matter in another way, C is so important to the life of the mother, and consequently to the life of the offspring, that the maternal need has the first claim. That is why according to Ingier [387, 405] when gravid guineapigs are fed on a diet deficient in C, the foetuses become affected within ten to twelve days with typical infantile scurvy. When the gravid guineapigs have been properly fed until near the time of delivery, a sudden transition to a scorbutogenic diet does not affect the foetuses, which

are normal at birth; but the milk is inadequate, and the offspring speedily become affected with scurvy. Pregnant animals put upon a scorbutogenic diet fall ill with scurvy more rapidly than non-gravid animals, and frequently die of the disease before delivery.

These considerations explain the facts observed by Figueira [1046] and by Dalyell and Still,[1055] who noted that infants at the breast may become affected with scurvy although the mother appears perfectly healthy.

As regards the C content of cow's milk in particular, Barnes and Hume [969] were the first to point out that the variations in the complettin content are subject to seasonal changes. The C content is highest from May to July, and lowest during the winter months. Hart, Steenbock, and Ellis,[1233] Hess,[1055] and Dutcher and his collaborators,[1330] likewise refer to this dependence of the richness of milk in C upon the seasons, and they regard the varying amount of C in the fodder as the essential cause of these changes. In spring and summer, when plants are in the most vigorous phase of their development, they contain comparatively large quantities of C; on the other hand, the ripening of hay is attended by a gradual decline in the amount of C it contains, which may be reduced to an inadequate proportion.

It is owing to this scanty supply of C in the milk that bottle-fed infants sometimes become affected with scurvy. Of course the customary practice of diluting cow's milk for the hand-feeding of infants lowers the percentage of C in the food to a dangerous extent, seeing that the C content of cow's milk is already low in many cases.[737]

Eggs contrast with milk as the first nutrient of a growing organism, in that they appear to contain very little C,[831] and certainly cannot cure scurvy.[750] In this poverty, they resemble seeds.

Fresh yeast [562, 737] is far more active than milk; but the autolysis of yeast destroys the complettin C,[491] though it has no effect upon vitamin and the growth-complettin.

c. Effect of Germination upon the C Content of Seeds.

We have already learned that seeds, which in the quiescent state contain so little C that they have no antiscorbutic

influence, develop large quantities of this complettin during germination. Consequently, an exclusive diet of germinated seeds is not scorbutogenic; and a supplement of germinated seeds to a scorbutogenic diet has prophylactic and curative effects.[102, 187, 203, 267, 735, 749, 841, 918, 972, 1057, 1066, 1118] In conformity with this we find that malt extracts, and especially the fresh watery extract of green malt, have antiscorbutic qualities.[533] The antiscorbutic substance in germinated seeds is not in the cotyledons, and still less in the primary rootlets; it is mainly found in the leaves, and the process of germination per se does not increase the C content of the seed. The antiscorbutic powers of germinated seeds is not fully developed until after the lapse of three days or more, when the formation of the first leaves has begun.[734] For this reason, the actual germ is inadequate in respect of C content,[491] whereas the leaves of the germinated seed are more effective than the entire germinated plant. If we wish to use the aggregate germinated seeds as a prophylactic nutrient, it is best to wait until the leaves have grown to a length of from half to three-quarters of an inch.[841] When germinated seeds have been dried, they no longer contain the antiscorbutic complettin.[93, 187]

4. Properties of the Complettin C.

It follows from the foregoing that the complettin C must be soluble in water. According to Hess and Unger,[751] and according to Harden and Zilva,[794] it is soluble in alcohol that is not too strong, and is therefore retained in the alcoholic solution when the fruit acids are precipitated from fruit juices by means of calcium carbonate and alcohol. Like the complettins previously considered, C has a fairly high power of resisting even strong mineral acids,[536] and a moderately acid reaction of the medium definitely favours the durability of the complettin[756]; but C is rather sensitive to alkalies.[536] However, as in the case of the growth-complettin B, the destructive effect of alkali is not immediately manifest, and complete destruction is not achieved for a considerable time.[899] The complettin C is not entangled in precipitates and carried down with them; and it cannot be removed from orange juice, for instance, by alumina or by a Chamberland filter.[688] In the preparation of Osborne and Mendel's protein-free milk,

C is retained by the milk, which does not lose any of its antiscorbutic power.[737] Like the fat-soluble complettin A, the water-soluble complettin C is sensitive to oxidising agents.[1055] This doubtless is the main reason why the storage of dried nutrients originally rich in C leads, even when the drying process has been carried out with the utmost care, to a rather rapid disappearance of the C content. From a further study of this matter we learn that dried vegetables suffer less from storage as regards their C content in proportion to the dryness of the air,[1304] so that the storage is best effected in the presence of phosphorus pentoxide. It is remarkable that Holst and Frölich [1304] have failed to draw the obvious conclusion as regards the mechanism of this reaction, which has an important bearing on our knowledge of the complettin: in the presence of air, the dried green vegetable substance has a catalytic action upon the aqueous vapour the air contains, leading to the formation of hydrogen peroxide, and this latter, which exerts an oxidising influence upon the complettin, destroys its characteristic antiscorbutic quality.

Reports vary concerning the thermostability of the antiscorbutic complettin. Holst and Frölich inform us that the boiling of cabbage, carrots, dandelion, and potatoes, reduces their prophylactic power [186]; and according to the same authorities [105] and also according to Plimmer,[1159] expressed cabbage juice is rendered inactive by boiling. Frölich [107, 204] found that raw milk in small doses did not prevent guineapigs from becoming affected with scurvy, but was able to cure the disease; this curative influence is greatly reduced when the milk has been heated to 98° C., and completely disappears after ten minutes' boiling at 100° C. I think, however, that the last statement must be an exaggeration, for the experiments of Nobel [1316] have shown that, even after one hour's boiling, milk contains considerable amounts of C, so that a double or treble quantity will cure infantile scurvy. According to Barnes and Hume,[969] milk still retains after boiling the power of protecting children against scurvy, provided only that the boiling has not been long continued and that after boiling the milk has been rapidly cooled.

According to Delf,[806] the antiscorbutic power of white cabbage is injured by heating; and she tells us [1115] that the

juice of green cabbage has its efficacy as an antiscorbutic notably reduced by twenty minutes' boiling, while by an hour's boiling about five-sixths of the antiscorbutic complettin are destroyed. In turnips, the C is more resistant to boiling,[1115] which seems easy to explain by the consideration that the heat cannot so readily make its way into the interior of the masses. The antiscorbutic qualities of germinating seeds are largely destroyed by boiling.[918] Exposure for from one to three hours to a temperature of 120° C. destroys the antiscorbutic faculty of all nutrients. There is general agreement that prolonged heating at a moderate temperature is far more noxious than brief exposure to a high temperature.[1066]

This makes it obvious why the pasteurisation of milk greatly reduces the C content of this nutrient,[411] and why infants and children fed on pasteurised milk are so apt to suffer from scurvy.[800, 1222] Of course in the process of condensation, the antiscorbutic qualities of milk are gravely impaired.[901] In young monkeys, a diet of condensed milk induces infantile scurvy [211, 249]; and in adult monkeys,[211] and also in guinea-pigs [885] it induces typical scurvy. Since the complettin C is sensitive to alkalies, we can readily understand that it is completely destroyed when milk is sterilised after the addition of sodium citrate, which has an alkaline reaction.[1289] Generally speaking, the sterilisation of nutrients impairs their antiscorbutic power, being more injurious in proportion to the height of the temperature.[741, 1025] Tinned meat and tinned milk are therefore invariably scorbutogenic [1194]; but vegetables with an acid reaction may still retain considerable antiscorbutic powers after cautious sterilisation.[899, 1194]

Since prolonged heating is in any case injurious, it is obvious that the drying of nutrients at a raised temperature must be extremely disadvantageous. Holst and Frölich [186] report that the drying of cabbage, carrots, and dandelion greatly impairs their antiscorbutic qualities; such efficacy as is retained by dried cabbage [749] is still preserved after brief heating at 100° C., but is completely destroyed at 110° C.[65]

Dried potatoes are likewise inadequate.[65] Givens and McClugage [1148] have made a thorough study of the effect of drying potatoes. They found that finely minced raw potatoes could be boiled for fifteen minutes without ill-effect, but that

their antiscorbutic efficacy was considerably impaired by one hour's boiling. The boiling is better borne when the water contains 0·5 % of citric acid. Potatoes dried in vacuo at a temperature ranging from 45° to 60° C. lost much of their efficacy ; and the greater part of the complettin was destroyed by drying in an air current for from six to eight hours at a temperature ranging from 35° to 40° C. ; subsequent brief boiling reduced the complettin content still further. Equally bad was the effect of drying for from four to six hours in an air current at a temperature ranging from 55° to 60° C. ; drying for from two to three hours at a temperature ranging from 75° to 80° C. destroyed almost all the complettin C. Preliminary treatment of the potatoes with 2 % acetic acid or 0·2 % hydrochloric acid for from eighteen to twenty hours before drying, had no influence. Four minutes' steaming of the minced potatoes before drying at a temperature ranging from 55° to 60° C. destroyed most of the complettin, and a subsequent brief boiling destroyed what was left. Potatoes baked in their skins for from forty-five to fifty-five minutes at a temperature of 204° C., then skinned, and dried at a temperature ranging from 45° to 50°C., could still prevent scurvy ; the skins of the baked potatoes no longer contained any complettin. These authorities infer that the destructive effect of the drying must be partly due to the influence of a ferment, seeing that less C is destroyed in proportion as the heating process is a rapid one. Here it is impossible to follow them, for were their reasoning correct, the preliminary treatment with steam should have given the best results, whereas this proved extremely destructive to the antiscorbutic powers of the potatoes. Though it was found that baked potatoes were still comparatively efficient as an antiscorbutic, we must not assume that this was because the heat was greater, and that the alleged ferment was thereby more rapidly destroyed, for the substance of potatoes has a low conductivity to heat, and within the time allowed for the baking the temperature in the interior of the tubers cannot have risen very high. Still, there may be something in Givens and McClugage's theory after all, for Delf and Skelton [807] state that cabbage does not forfeit its antiscorbutic virtues so completely on drying when, as a preliminary, it has been dipped in boiling water.

According to Givens and Cohen,[754] in cabbage and potatoes C bears a quick but careful drying so well that the dried product is still effective as an antiscorbutic; but prolonged drying, especially at a considerable heat, completely destroys the complettin. From tomatoes, according to Givens and McClugage,[838] a dried product that is still effectively antiscorbutic can be prepared.

Owing to the acidity of lemon juice, the C in this juice will bear an hour's heating at 100° C.[105]; and in the case of orange juice [1109] and lime juice,[1177] cautious evaporation to the consistency of a syrup does not impair the activity. Basset-Smith [1249] was able to prepare a very active dried product by boiling fresh lemon juice for five minutes, cooling, and condensing in vacuo at an ordinary temperature to a specific weight of 1·3; he thus secured a strongly acid viscous fluid which could be made into tablets with lactose, or some similar vehicle. Hawk, Fishback, and Bergeim [1058] were able to secure an active dried product from orange juice by evaporating it to dryness in vacuo at an ordinary temperature. According to Harden and Zilva,[794, etc.] the precipitation of the fruit acids with calcium carbonate and alcohol does not impair the antiscorbutic efficacy of lemon juice, but the juice now rendered neutral is injured by subsequent preservation for fourteen days at an ordinary temperature, and is injured still more by evaporation in vacuo at a temperature ranging from 30° to 40° C. The untreated juice bears such concentration very well, and so does the juice after precipitation of the acids if it be at once weakly acidulated with citric acid.

Delf,[1115] who has made an exhaustive study of this question, finds that orange juice in its natural state of acidity can well bear heating for an hour at a temperature ranging from 70° to 100° C., and that even after the juice has been heated for an hour at 130° C. it is merely necessary to double the prophylactic dose. In orange juice the thermostability of the complettin is therefore twice as great as in expressed turnip juice. But even when the acidity of the orange juice has been reduced to correspond with the low acidity of the expressed turnip juice, the thermostability of the C in the former is still retained, and it is therefore not due to the strongly acid reaction of the juice. Orange juice that had

been heated in sealed tins for from twenty to thirty minutes at a temperature ranging from 80° to 100° C. was found to be still fully effective as an antiscorbutic after five months.

Nevertheless, it seems undesirable to trust to the antiscorbutic efficacy of stored products. The antiscorbutic power of expressed cabbage juice,[105] lemon juice,[794, 1066] and orange juice,[751] seems to disappear in consequence of prolonged storage. Perhaps the cause of this degradation is not so much a primary instability of the complettin as its sensitiveness to the oxidising influence of the atmosphere. This, we may presume, explains Delf and Skelton's observation,[807] that the storage of dried cabbage for from two to three weeks reduced its C content by about nine-tenths, and that three months' storage completely destroyed its antiscorbutic efficacy.

The complettin seems to be peculiarly unstable in germinated seeds. I have more than once mentioned that in these C is destroyed by brief boiling. Drying also destroys it completely.[102, 1166, 1345] The soaking of other dried vegetables appears to be very injurious to the C they contain.[1199]

Barnes and Hume state that the drying of milk reduces its antiscorbutic efficacy to about two-fifths of the original. But the extent to which this reduction takes place varies with the method of desiccation, for Hess and Unger [899] report that milk transformed into an absolutely dry powder within a few seconds at a temperature of 116° C. by the Just-Hatmaker process was still fully efficient. In Germany, similar results have been secured by the use of the Zetror apparatus of the Benno-Schilde Company. Especially valuable, from this point of view, is the Krause method of producing dried milk, which from the descriptions would seem to be identical with the American.

According to Hess and Unger,[751] the most actively antiscorbutic vegetables lose their efficacy on drying. Erich Müller [800] refers the outbreak of scurvy in the Rummelsburg orphanage to the use of milk that had been twice pasteurised and to the use of the dried vegetables of commerce. The latter were especially deleterious thanks to their having been bleached before drying, and having thus lost their excess of bases. A cure ensued upon the giving of milk that had only

been once pasteurised, together with fresh vegetables. [I doubt if it can have made much difference whether the milk had been once pasteurised or twice, seeing that a single pasteurisation suffices to destroy the C of milk, which in any case contains rather a small quantity of this complettin.]

Manifestly the German practice of bleaching vegetables before preserving them, and especially before putting them on the market in a dried state, is extremely undesirable. Not merely do the vegetables forfeit their excess of bases; but since the complettins C and B and the antineuritic D are all readily soluble in water, they are dissolved out in the first boiling.[899, 1087, 1278]

5. Composition of the antiscorbutic Complettin C.

A chemist may be forgiven for inability to refrain from acting after his kind, and for the involuntary attempt to draw, from the available data, conclusions as to the composition even of substances that have not yet been isolated! The behaviour of the complettin C is so characteristic that we can, in fact, with some degree of certitude predict at least one peculiarity of its composition. First of all, this complettin is thermolabile. We know of a large number of chemical changes which ensue when the substances are warmed. Let me mention a few of them. Ketones and aldehydes can undergo transformation into the corresponding enol forms. Alcohols containing several hydroxyl groups in at least a γ relationship to one another, or oxi-acids in which hydroxyl and carboxyl are separated from one another in like manner by at least two carbon atoms, and similar amino-acids, can be transformed into anhydrides with the splitting off of water or ammonia, and cyclopoeisis. Unsaturated compounds, especially such as contain two conjugated duplex compounds (separated by a simple link), will, on being warmed, very readily combine with a molecule of water, in conjunction with the formation of simple unsaturated compounds. And so on.

The extraordinary sensitiveness of the substance to oxidation has been repeatedly referred to. The complettin becomes inactive when a fluid containing it is stored, and still more when a dried nutrient containing it is stored, with

free access of moisture and air; it is also rendered inactive by direct oxidation, as for example by the action of hydrogen peroxide. This fact, too, justifies certain conclusions as to its composition. One possibility is that it contains readily oxidisable molecular groupings like those of the ketones or the aldehydes. Another possibility is that of duplex combinations, which are sometimes readily oxidisable. Especially sensitive in this respect are, once more, the conjugated duplex compounds, which undergo transformation into dioxy-compounds under the influence of mere traces of hydrogen peroxide, thus: $R . CH : CH . CH : CH . R' + HO . OH =$

$$R . CH_2 . CH(OH) : CH(OH) . CH_2 . R'.$$

It is characteristic of such conjugated compounds that when stored for a long time in the presence of moisture and air, and rapidly when the temperature is fairly high, they take to themselves traces of hydrogen peroxide formed in the aqueous vapour, and thus by degrees are transformed into an entirely new substance. The process is favoured when the body under consideration can itself play the part of a catalase (as so often happens with the terpene derivatives), or when other oxygen conveyers are found in the mixture. This state of affairs obtains in plants, and in the majority of fresh animal tissues; in both cases there is present more or less catalase; furthermore, animal tissues contain haemoglobin, and vegetable tissues contain chlorophyll, both of which are oxygen conveyers.

We have already seen that by rapid heating at a high temperature and subsequent drying at a low temperature, the keeping qualities of the product are favourably affected; and we have drawn the conclusion that an enzyme may perhaps contribute to the decomposition of the complettin in the dried preparation. We have learned that prolonged heating at a comparatively low temperature ranging from 30° to 40° C. is more injurious to the integrity of C than boiling it for as long as an hour. We know, moreover, that the substance is extremely sensitive to the action of the oxygen of the air, but that this sensitiveness is much less marked when the air is perfectly dry.[1304] *From all these considerations we are inclined to draw the conclusion that the complettin C is probably a conjugated duplex compound.* Furthermore, the

idea is supported by the fact that the substance is rendered inactive by temperatures over 110° C., for at high temperatures many dien compounds are converted into monin compounds. ($— CH = CH — CH = CH_2 —$ becomes $— CH_2 — C \equiv C — CH_2 —$). The behaviour of the substance when exposed to ultraviolet light confirms the idea. When ultraviolet light acts on damp air-containing substances, hydrogen peroxide is formed, and this is fairly stable in weakly acid solutions, whereas it is extremely unstable in alkaline solutions. Zilva [916] tells us that ultraviolet light in weakly acid or in neutral solutions has very little influence upon the antiscorbutic complettin, but speedily renders the complettin inactive when the solution is weakly alkaline.

Of course these hypotheses do not exclude the possibility that the substance may also contain other unsaturated groups which may lose their activity in some other fashion through the operation of heat.

Beyond this, we have nothing positive to say regarding the nature of the antiscorbutic complettin. Delf [806] has suggested that we may have to do with a special enzyme, seeing that it is sensitive to temperatures which denature the proteins. But outside the living body, it is just as sensitive to the much lesser heat which is the optimal temperature for warm-blooded animals, and we are therefore led to infer that the process whereby it is rendered inactive when heated must be of a different nature. Fürst [187, 203] declared a good many years ago that this complettin could not be indentical with any of the familiar forms of proteins, fats, carbohydrates, salts, or enzymes.

Funk [205] seems to have been inclined at the outset to believe that C was identical with his vitamin, and Freise [391] regarded it as at least akin to the vitamins. This theory was to some extent supported by the frequency with which beriberi is complicated with scurvy,[1165] and also by the fact that in preparing the vitamins small quantities of C are precipitated with these. Subsequent investigation has, however, shown beyond a doubt that we have no justification for assuming the identity of the two classes of complettins, for they differ extensively in respect both of chemical properties and of physiological effects.

The non-identity of C with the fat-soluble complettin A has been established by a large number of investigations.[491, 750, 751, 754, 805, 831, 1194] So has its non-identity with B.[491, 1116, 1153, 1194]

At this juncture, therefore, we can say nothing definite as to the nature of the antiscorbutic complettin.

6. The physiological Consequences of C Deficiency.

a. Clinical Picture.

Thus when there is a lack of C in the diet, a characteristic illness arises, the disease known as scurvy. In minor cases, those running a subacute or chronic course, scurvy is often confounded with other disorders; for example, many slight cases of infantile scurvy are mistaken for rickets. The symptoms of the initial stage are anaemic and cachectic manifestations, such as loss of weight, fatigue, drowsiness, disinclination and incapacity for work, mental depression, peevishness, etc. The emaciation makes rapid progress, and at the same time the skin becomes pale, flaccid, and remarkably dry. There are pains in the joints, especially in those of the lower extremities. In this stage the disease may remain arrested for a considerable period; and since in children during the phase of growth there occur in scurvy disturbances in the normal process of bone formation, it is not surprising that the illness should be confounded with incipient rickets. But even in this early stage there are pathognomonic symptoms in the form of haemorrhagic manifestations, which in subacute and chronic cases of scurvy strongly resemble those of purpura.

In typical attacks, after about a fortnight the signs of the haemorrhagic diathesis become conspicuous, there being in most cases a characteristic affection of the gums. These become bluish at the edges, and are greatly swollen, so as to project around and between the teeth. The tumefied gums are extremely sensitive, bleed at the slightest touch, and soon begin to ulcerate. As the swelling increases, the gums become necrotic, and assume a whitish or a brownish-black tint here and there, the ulcers being coated with evil-smelling

greyish-white masses. The teeth are loosened and decayed; mastication is impossible; the breath is horribly foetid. Whereas in purpura, the haemorrhages begin in the subcutaneous tissue, and only extends by degrees to the gums and the rest of the buccal mucous membrane, in scurvy they are concentrated around the teeth and around neglected roots, so that the observer has the impression that the trouble starts from the teeth. Apart from the affection of the gums, the signs in the mouth are merely those of slight stomatitis with moderate swelling and a little bleeding. In severe cases there ensue, to the accompaniment of moderate febrile manifestations, other haemorrhagic symptoms, such as purpuric patches on the skin, intermixed with lichenoid or herpetiform eruptions, large ecchymoses, and also non-haemorrhagic bullae. In contradistinction to purpura, the eruptions in scurvy have a strong tendency towards ulceration, the ulcers being large and sluggish; sometimes they are very deep, and when they are situated in the flexures of the joints they are apt to lead to contractures should the patient recover and cicatrisation occur. Haemorrhages may occur in various other parts; when they are superficial, they are prone to suppurate, are extremely painful, and are often attended with considerable irregular pyrexia. Should there be any preexistent scars in the bones (the seats of old fractures) these are apt to soften. In many cases, the articular ends of the bones and the cartilages of the joints become diseased and the synovial membranes grow dry, and these changes may lead to permanent stiffness of the joints. The bone affections may even result in the complete separation of epiphyses. Sometimes, generally as an early symptom, there may be severe haemorrhages from the mucous membranes like those that occur in haemophilia; among these, epistaxis is the most common.

b. Pathological Anatomy.

The haemorrhagic symptoms are not difficult to explain on the supposition of a change in the walls of the capillaries, perhaps accompanied (as in haemophilia) by a disturbance of the process of coagulation of the blood. On the other hand, there is as yet no explanation of the characteristic affections of the bones, which enable us after the lapse of thousands of

years to ascertain from an examination of the skeleton that the person to whom it belonged had died of scurvy, or else had recovered from a severe attack of the disease. There are no other organic changes of a specific nature. The atrophy of the glands and the general emaciation, do not differ in any way from what we see in other grave disorders of nutrition; and we may assume that they arise because a scorbutogenic diet is usually poor in B as well as in C, so that they are not in any way peculiar to C deficiency. Furthermore, though oedema is common in scurvy, it is common in all the deficiency diseases, and is therefore nowise characteristic of a lack of the antiscorbutic complettin.

Owing to the atrophy of the glands, there is an arrest of the digestive secretions. In severe cases, there is complete achylia, and the salivary secretion is greatly diminished, having usually a strongly acid reaction.[640] These secretory disturbances naturally favour the onset of gastro-intestinal disorders as complications. On the other hand, everything which makes a special claim on the bodily activities, predisposes to the disease, and this statement especially applies to intestinal disorders,[1066] a deficiency of the food in calories, febrile disorders,[1009] and vigorous growth.[1087, 1278] As in the case of the other deficiency diseases, the adrenals are exceptions to the general rule of glandular atrophy, for they undergo hypertrophy, while also exhibiting a partial fatty degeneration, especially of the cortical layers.[1177, 1222]

Except for the reduction in the number of erythrocytes which is characteristic of the haemorrhagic diathesis and especially of its haemophiliac forms, changes in the blood are not conspicuous. There is, indeed, almost invariably a decline in haemoglobin richness,[1242] such as is usual in anaemic states; and there is an increase in the urea.[577] Although the resistance of the organism to infections is so greatly reduced, the C deficiency does not lead to any changes in the serological constants of the blood.[917, 1222]

As regards metabolism, the nitrogenous balance is usually negative, and, in acute cases at least, there is retention of phosphorus and calcium—but these manifestations are not especially characteristic of C deficiency. All the patients, at any rate in the early stages, and as long as the mental

debility has not become excessive, exhibit a vigorous craving for fresh nutrients, whether meat, milk, fruit, or vegetables.[1009] McClendon [1129] is certainly right when he insists that in a state of nature this craving must be one of great survival value for men and animals. Among the American soldiers in the trenches, when their rations were restricted to chocolate, eggs, dried milk, and sugar, worked up into a sort of biscuit, he noted that this craving became overpowering within two or three days, and led them to refuse their rations.

The need for the antiscorbutic complettin varies greatly in different species of animals. Prairie dogs [1300] and rats have a very low requirement, and can live for long periods on a diet containing no C; on the other hand, some of the other rodents (rabbits and guineapigs, for instance) are extremely sensitive to a lack of C in the diet. Characteristic in this respect is the fact recorded by Harden and Zilva [1105] that for a guineapig weighing a few hundred grammes the same prophylactic dose of C is requisite as for a monkey weighing two or three kilogrammes. Furthermore it would seem that young animals of the same species vary in their requirements, and this has led some authorities to formulate the hypothesis that at birth animals must bring with them from their mother varying stores of C, the difference between one litter and another depending upon the supply of C to the mother during pregnancy.

c. Reciprocal Relationships between C and inorganic Substances.

Our account of this matter would be incomplete unless we drew attention to the fact that the full efficacy of C cannot be developed unless the diet contains inorganic salts in suitable proportions. Holst and Frölich [65] state that calcium salts are useless in scurvy unless C be also supplied, but that a lack of calcium interferes with the rapid and effective action of C.

There can be no doubt that the onset of scurvy is facilitated by the circumstance that most of the nutrients which prove to be scorbutogenic are deficient in inorganic bases as well as in C. When Fürst [102] says that nutrients whose ash is alkaline can also give rise to scurvy, an error underlies this assumption that the inorganic bases are of no value in nutrition. All the ash analyses quoted by Fürst are fallacious,

for recent investigations have shown that the nutrients (peas, lentils, and almonds) to which he refers, contain an excess of acids, this excess being especially marked in the pulses. On the other hand, we have a report from Funk [527] to the effect that in certain cases of scurvy the administration of sodium bicarbonate has proved useful. Some of the features of the pathological anatomy of this disease, especially the bone disorders and the oedema, indicate that acidosis must play a part in its production.

Florence [1156] has published a speculative paper in which he contends that a lack of sulphur may perhaps play a part in the causation of scurvy and infantile scurvy. Although this writer has not done any experimental work in order to corroborate his theory, there may be some truth in it, for many of the scorbutogenic nutrients, and the cereals in especial, contain inadequate quantities of cystein; others, such as meat, part with some of their sulphur when strongly heated, and thus become inadequate in this respect. Perhaps such a lack may in part explain the malnutrition.

d. Forms of Purpura in relation to C Deficiency.

The various forms of purpura, and especially purpura simplex, are to-day regarded by physiologists as the outcome of chronic malnutrition due to C deficiency. This theory is confirmed by the fact that the most successful treatment of purpura simplex is dietetic. Although serum, gelatine, and calcium salts, are sometimes given by injection in the hope of increasing the coagulability of the blood, the value of these remedies is much disputed. As regards diet, lemons and other raw fruits, salads, and green vegetables, are found to be the most useful nutrients. In purpura simplex a cure can be effected by these means without confining the patient to bed, but absolute rest in bed is essential in the graver forms of purpura haemorrhagica if extensive extravasations are to be avoided.

6. Mode of Action of the Antiscorbutic Complettin.

No definite opinion can as yet be uttered regarding the mode of action of C in the animal organism. In scurvy, as

in most of the deficiency diseases, there is probably a complex of causes at work; for instance, the peculiar "fragility" of the tissues upon which the liability to haemorrhages depends is probably favoured by acidosis. But the latter cannot be the main cause of the disease, for, as we have repeatedly had occasion to note, scurvy may arise when the diet is rich in bases.

The bone diseases characteristic of scurvy bear a certain resemblance to those which occur as a sequel of A deficiency. The similarity is, however, very superficial; and the two complettins, A and C, are sharply distinguished one from the other, especially by their behaviour towards alkalies. We might rather be inclined to look upon acidosis as the cause of the bone disorders, but we have seen that acidosis cannot be regarded as the main factor of scurvy.

The negative nitrogenous balance, the ulcers, etc., might be ascribed to a deficiency of the growth-complettin B, but we have already learned that this complettin is not always lacking in scorbutogenic diets.

We have, then, to do with a characteristic syndrome dependent upon a deficiency of an unknown substance or class of substances to which we give the name of the complettin C. But it remains dubious whether all the phenomena of scurvy can as yet be comprised under a unified outlook.

CHAPTER EIGHT

MALNUTRITIONAL OEDEMA

1. Clinical Picture.

In the accounts of the deficiency diseases previously considered, oedema has frequently been noted as a complication, and we have seen that in certain circumstances it may attain such proportions as to dominate the clinical picture. This happens, for instance, in the case of wet beriberi. I have, however, been careful to point out that the oedema was no more than accessory, and was not an essential feature of the disease. There are, however, many facts to indicate that oedema may occur from defective nutrition as a primary disorder. In France, and still more in Central Europe, during the war malnutritional oedema came to be recognised as one of the consequences of wartime feeding, and has now to be described as an independent clinical entity. We shall find that experience gained in the study of the other acomplettinoses will be of considerable value in this connexion; and, on the other hand, that an accurate study of malnutritional oedema will throw light on the etiology of the other acomplettinoses.

Apart from local oedema, due to local causes or to such nervous disorders as hysteria, it has been customary to recognise three varieties of oedema, dropsy, or anasarca, which often pass into one another, though in isolated cases they may appear to constitute distinct types. First of all there is renal oedema, due to the blocking of the uriniferous tubules in consequence of degenerative changes in the kidney tissues, or in exceptional cases to grosser mechanical obstructions such as those caused by renal calculi. Secondly we have the passive oedema that arises from an insufficiency of the arterial walls, perhaps from organic changes in these (hyaline

degeneration), or it may be caused by an abnormal fall in blood-pressure. Sometimes passive oedema may be due to a mechanical relaxation of the walls of the bloodvessels, especially when they are not sufficiently aided by the surrounding muscles, as happens to those who sit or stand for excessively long periods when at work in factories, shops, or offices. When passive congestion has lasted a long time, it may react upon the heart, which has more work thrust upon it in the attempt to drive the blood through the relaxed and dilated vessels. Thus we get a transition to the third form, which is known as cardiac oedema. In cardiac oedema, the heart has failed, it may be for the reason just mentioned, it may be from inborn weakness or from congenital or acquired organic defects, or it may be as a complication or sequel of other illnesses, toxaemias, etc. However originated, cardiac oedema is the outcome of a failure of circulation.

Owing to the arrest of the blood-stream in passive oedema or cardiac oedema, and owing to the great increase in the content of the bloodvessels in renal oedema, the vascular walls suffer, and they allow serum to transude into the environing tissues. This extravasated fluid accumulates especially in the comparatively inert subcutaneous tissues, which may be thus swollen beyond recognition, but in part it infiltrates the tissues of the other organs. In advanced cases, it accumulates also in the various body-cavities—the joints, the peritoneal cavity, the pleural cavities, the pericardial cavity, etc.

All the varieties of oedema we have considered in connexion with the deficiency diseases, belong to the class of the passive oedemas. In exceptional instances only, as in severe cases of beriberi or scurvy, the passive oedema may somewhat suddenly pass over into cardiac oedema, this being a sign that the heart has become exhausted. The appearance of cardiac oedema in the fulminant form of beriberi therefore justifies a very grave prognosis, for death may occur at any moment from heart failure. But malnutritional oedema, known in Germany as "Hungerödem" (famine dropsy) is of a very different type, for here the oedema takes the form of an independent disease. First, then, we must study the clinical symptoms and the pathological changes which entitle us to look upon the disease as an independent entity.

Numerous reports are available for this purpose, based for the most part on the work of German investigators.

According to Jansen,[684, 1061] and to Bürger,[902, 1217] apart from the dropsical effusion in the subcutaneous tissues and in the various organs and cavities of the body, the most prominent symptoms are bradycardia, anaemia, and hydraemia, polyuria and nycturia, a lowering of blood-pressure to 65 mm. or less, hemeralopia, and a lowered temperature. Schittenhelm and Schlecht[909] draw special attention to the marked slowing of the pulse during repose. In most cases, too, there is extreme emaciation.[902]

2. Pathological Anatomy.

The most notable features on post-mortem examination are the almost complete disappearance of the fatty tissue, even in the case of the viscera,[909] and the atrophy of the parenchymatous organs.[1037, 1061, 1240] In especial the heart and the liver are very small, and sometimes show signs of brown atrophy. The liver and the muscles are as a rule lacking in glycogen. Jansen stresses the atrophy of the thyroid. The activities of the pituitary body and the adrenals are arrested [1037, 1316]; the adrenals are usually hypertrophied. McCarrison actually declares that in oedema he has found the adrenals thrice the usual size, but he is probably referring to cases of beriberi.[1215]

The most notable characteristic of the blood is hydraemia. In consequence of this, the refractive index is greatly reduced [716, 1217] and the specific weight is also much lowered. The dried residue may be as little as 20 % or even 15 % of the aggregate blood.[1217] As a rule, the water is about 10 % above normal, and therefore the protein concentration is reduced both relatively and absolutely.[716] On the other hand, the residual nitrogen may be normal, or may be increased by as much as 30 %.[716, 911, 1061, 1217] Feigl[716] found in patients strictly dieted in institutions that there was hypoglycaemia to an average extent of 40 %, but that when the patients were able to feed as they pleased the ratio of sugar in the blood was extremely variable. Schittenhelm and Schlecht found that the sugar content of the blood was usually normal, but sometimes rose to 0·26 %[911]; on the other hand, in one

case Jansen found that there was only 0·03 %. The fatty acids in the blood are considerably reduced,[716] and so is the aggregate fat.[1217] According to Jansen,[1061] the urea content is normal. The lipoid phosphorus is reduced,[1061, 1217] but the acid phosphorus is increased. The haemoglobin richness of the blood varies greatly, and so does the blood-count both of the erythrocytes and of the leucocytes. The acetone content of the blood is always somewhat increased.[716]

According to Feigl,[716] there is in most cases an increase in the kreatin richness of the blood, at any rate in the early stages of the disease, but a decline in the kreatinin richness. In conformity with this he finds, as a rule, an increased ammonia richness. Relatively, the free cholesterin in the blood is usually increased, though there may be a decline in the absolute quantity. Cholesterin ester is found in abnormally small quantities. There is sometimes a moderate increase in the amounts of sodium chloride, calcium, and sulphates; but there may also be a falling-off in the amount of calcium. Iron, and especially calcium, are sometimes notably diminished. [These reports are far from being adequate to the contemporary standards of inorganic analysis !]

Very little information has been published regarding the composition of the urine in cases of malnutritional oedema. All investigators are agreed that the acidity of the urine is extremely variable. In a research of my own, I found a great increase in the ammonia richness of the urine (the ammoniacal nitrogen amounting to 67 % of the total nitrogen) with a reduction in the urea richness. A little acetone was present. Feigl [716] also points out that the urine usually contains kreatin.

Corresponding with the atrophy of the glands, there is a great falling-off in the activity of these organs, and in cases of long duration there may be achylia.[902] This explains the frequent occurrence of gastro-intestinal disorders as complications.[902, 1037, 1056, 1217]

3. Prognosis.

Generally speaking, the prognosis is favourable, unless cardiac oedema should develop, which is followed by death

from heart failure. The first essential of treatment is rest in bed. Next in importance comes a change of diet, but views as to what should be the nature of this change vary fundamentally, the variations depending on the differences of opinion presently to be discussed concerning the dietetic factors of the disease. Some insist that the supply of proteins should be improved; others emphasise the importance of a better supply of fats or carbohydrates or both. Some think that to increase the vitamin in the diet is of no avail; others stress the need for the provision of a sufficiency of B; and so on.

4. Metabolism.

a. Nitrogenous Metabolism.

Passing to consider the details of metabolism in this illness, we find Nixon [1258] reporting that the nitrogenous balance is maintained. Jansen [1061] and Bürger [1217] found a negative nitrogenous balance in cases where the supply of fats and carbohydrates was inadequate, and Bürger claims to have noted a moderate decline in the protein turnover. This last may perhaps be connected with the fact observed by Schittenhelm and Schlecht [912] that in persons suffering from nalnutritional oedema the organism manifests an intense nitrogen hunger, and that for this reason the utilisation of the proteins in the food is comparatively effective. No notable abnormalities have been noted in the fat or the carbohydrate metabolism. Observers have been unanimous in recording a markedly negative calcium balance; and Bürger also refers to the phosphorus balance as negative.

b. Sodium-Chloride Metabolism.

As in all varieties of oedema, interest has been mainly concentrated upon the sodium-chloride metabolism. But in this connexion the medical publications referring to the matter have repeatedly displayed lamentable ignorance of long-familiar facts concerning the way in which the various ions act on the urinary apparatus. For more than thirty years we have known that the sodium ion has a paralysing effect upon the activities both of the kidneys and of the ureters,

and according to the more recent (though not so very recent) researches of American physiologists, this is equally true of the chlorine ion. Röse, moreover, has proved by experiment [69, 70] that when the organism is poor in sodium chloride, dosage with this salt reduces the excretion of urine. The discoveries of Magnus-Levy [1163] have therefore done no more than confirm facts that have long been established. In my own writings I have always insisted that the excretion of sodium chloride is a slow business, and that in persons who have been accustomed to consume an abundance of common salt, months or years of deprivation must elapse before the stores of sodium chloride in the body are depleted. It may therefore be taken as a matter of course that when oedema sets in in a person whose diet contains a liberal supply of common salt, there will always be a retention of this substance in the body. As a matter of experience, all observers are agreed that in malnutritional oedema there is a retention of sodium chloride by the body, and that when the oedema subsides there is a profuse excretion of the salt. Bürger noted [902] that when the oedema was setting in, there was marked craving for sodium chloride, although as much as 12 grammes were being consumed daily. The explanation doubtless is that during the onset of malnutritional oedema, as during that of all the maladies dependent upon an ill-balanced diet, there gradually arises a loss of appetite, and sometimes a positive loathing for food; the patient then attempts to stimulate appetite by over-seasoning the food.

For the rest, it would seem that sodium-chloride metabolism is normal during malnutritional oedema; and Schittenhelm and Schlecht's observation [910] that elimination of the salt is somewhat retarded in this disease, serves merely to confirm the fact. Knack and Neumann,[639] Jansen,[1061] and Rothstein [1032] are agreed that the isolated administration of water does not promote the retention of water, and that the isolated administration of sodium chloride does not promote the retention of sodium chloride; only when sodium chloride is given in watery solution, does there occur a retention of both water and sodium chloride.

5. Dietetic Factors of the Disease.

a) The pathogenic Diet.

Opinions are diametrically opposed concerning the nature of the pathogenic diet. There is hardly an assertion in respect of this which is not disputed by some rival authority. It is obvious that the personal bias of the various writers has played a considerable part in dictating their respective assertions; what one describes as an abundance is referred to by another as a quite inadequate quantity. Most observers are agreed in stating that the calorie content of the pathogenic diet is too low [684, 902, 1217, 1258]; but according to Schittenhelm and Schlecht,[912] this has not always been the case. We are often told that the supply of protein has been too small,[902, 912, 1196, 1225, 1258] the daily amount ranging in these instances from 41 to 74 grammes. According to Liebers,[1079] however, the protein content of the diet was sufficient: in peacetime the amount of protein in the hospital diet has been 77·33 grammes; in 1916, it fell to 50·53 grammes; in 1917, it was 60·26 grammes; and in 1918, it was 71·05 grammes.

Many authorities incline to regard an excess of carbohydrates in the diet as injurious [902, 1217]; but Jansen [684] reports a cure by a liberal supply of carbohydrates. Others consider that the fats in the food were deficient.[912, 1064] According to Bürger,[1217] it was not always possible to demonstrate that the supply of inorganic salts was inadequate.

German writers in general are agreed in insisting that there seemed to be no lack of complettins in the diet [639, 902, 912, 1064, 1225, 1258]; whereas the British authorities refer to the lack of accessory food factors [1037, 1056]; and according to Bürger [1217] the complettin content of the food was primarily low, and the deficiency was often exaggerated by faulty methods of preparation. Kohman [1086] and Nixon [1258] stress the disproportion between the richness of the food in water and its lack of solid constituents. Kohman, working alone and also in collaboration with Denton,[784] saw dropsy arise in cases in which carrots were being consumed in conjunction with an abundance of fat or starch, but in which a cure resulted on the administration of casein and calcium salts. The reports of H. de Waele [1196] and Bürger [902] contain typical

instances of diets leading to malnutritional oedema. According to de Waele, in a French almshouse the diet consisted of soup and bread, or soup and potatoes, with beans and fat twice a week. In Bürger's cases, the pathogenic diet was composed of bread, vegetables, and a small quantity of potatoes, with a little lard, and small amounts of pickled or salted meat.

There is general agreement that strenuous physical labour predisposes to the disease. Bürger[902] (see also [1217]) states that among persons consuming the same amount of calories, those who did the hardest work were the first to fall ill; and that when the supply of calories varied, the persons whose diet was most deficient in this respect were the first to become affected with the disease. As in the case of scurvy, predisposition arises from anything which increases the bodily needs (hard work, very cold weather,[639] febrile disorders), and from anything which tends to hinder absorption (gastro-intestinal disorders).

b. Wartime Feeding.

Sporadic cases had occurred earlier but malnutritional oedema first assumed an epidemic prevalence in Germany during the summer of 1917,[1003] when the diet of the people was characterised by a lack of fats, high-grade proteins, potatoes, and fresh vegetables, except for kohlrabi, which was abundant. During the subsequent years, the general diet, and especially the diet in institutions, was still greatly lacking in fat, high-grade proteins, potatoes, and fresh vegetables, whereas cereals (which had to a considerable extent been degraded in value—see above p. 211), kohlrabi, and very poor soup-powders or soup-tablets, and dried vegetables, predominated. To complete the picture it is necessary to mention that as a rule, and doubtless invariably in institutions, the boiling of the kohlrabi was excessive, and that the water of the first boiling was thrown away; also that in the factory preparation of dried vegetables, the fresh vegetables had been treated with steam before drying.[1509] We must remember, moreover, that the abundant consumption of kohlrabi induced in many instances severe intestinal irritation, whereby the utilisation of the food was greatly impaired.

c. Prison Dropsy.

So-called famine dropsy or malnutritional oedema is by no means a new disease. As long ago as 1907, Holst [65] pointed out that, in the beginning of the nineteenth century, dropsy was exceedingly common in the jails of Europe and North America (see also [1554]), so that, among the causes of death in prison, dropsy sometimes took the first place. Bigland,[1037] who studied malnutritional oedema among prisoners of war in Egypt, was able to compare the disease with the famine dropsy he had seen in India, where it has long been known that dropsy is a common sequel of the frequently recurring famines.

d. Ship Beriberi.

Holst and Frölich,[65] who have studied the old reports concerning prison dropsy, consider it to have been identical with the so-called ship beriberi. Rumpel and Knack [571] have come to the same conclusion. Nocht,[43] who is the greatest authority on ship beriberi, gives a description of it which assimilates it in every respect to famine dropsy. It always runs a chronic course, and even in the comparatively rapid cases it lasts for several weeks at least. The initial symptoms are nausea, lost of appetite, constipation, and general debility; then comes the characteristic oedema, beginning in the feet and ankles, and slowly but surely spreading upwards. Ultimately, owing to the extensive swelling and the consequent palpitation and dyspnoea, the patients are forced to take to their beds, and die from heart failure. Associated symptoms in many cases are severe gastric discomfort, gastralgia, and even haematemesis. Among nervous symptoms, hemeralopia is common, and there may be also slight paraesthesias in the feet and legs. True paralysis is rare, and when it occurs may perhaps be due to a complication with genuine beriberi; just as an eruption of vesicles in the mouth, and the tendency to moderate haemorrhages, sometimes seen in ship beriberi and famine dropsy, suggest a complication with scurvy. The only point in which ship beriberi resembles true beriberi is the occurrence of paraesthesias in the former as well as the latter, but these are by

no means characteristic. Everyone who has to sit still for a long time is familiar with the onset of such paraesthesias, which may become intolerable even in healthy persons.

This description of ship beriberi seems a mere plagiarism from the description of famine dropsy. There can be no doubt that prison dropsy, ship beriberi, and the malnutritional oedema of the war years and of the Indian famines, are one and the same disease. The treatment which is found most useful for ship beriberi confirms this supposition, for here likewise rest in bed is the first essential and change of diet the second. Just like the patients suffering from malnutritional oedema, those affected with ship beriberi recover with marvellous rapidity, so that they can be discharged from hospital in a week or two, and in slight cases can even resume their work on the ship after four or five days. In 1908, at the first congress of the German Society for Tropical Hygiene, Nocht [74] pointed out that even in Germany attacks of illness resembling ship beriberi were by no means rare, and must be due to defective nutrition.

A. W. McCann [1554] gives a graphic description of the fate of the German accessory cruiser "Kronprinz Wilhelm," which, after a raiding voyage which had been successful for two hundred and fifty-five days, had to surrender to internment in the United States because the spread of ship beriberi among the crew had made it impossible to manoeuvre the vessel any longer. But McCann is mistaken when he supposes that wholemeal could have prevented the trouble, for then scurvy would have taken the place of malnutritional oedema. This warship was conquered by the food-preserving industry!

The diet which induces ship beriberi is closely akin to that which causes malnutritional oedema. It consists of flour and bread, peas or beans, dried potatoes, tinned or salted meat, and preserved vegetables. In German experience the disease usually makes its appearance on shipboard when the store of fresh potatoes has been exhausted, and the crew has had to be fed on dried potatoes for a time. Holst and Frölich [65] and Schaumann,[122] who record this observation, state also that the continued diet of preserved foods soon becomes so distasteful, that many of the crew restrict their consumption to a few articles (especially bacon, bread, meat,

and preserved vegetables), so that a diet already ill-balanced is thereby yet more restricted. The same phenomenon has been noted in many cases of malnutritional oedema in Germany. Moreover, every doctor will be able to recall from his personal experience the cases of a number of neurasthenic patients who lived on some such extremely restricted diet in the conviction that they could not tolerate other foods.

Ameulle [1228] maintained as recently as 1920 that malnutritional oedema in Germany occurred only among the prisoners of war. This gross misstatement must, of course, be ascribed to the war psychosis, by which, unfortunately, other noted scientists have also been afflicted.

6. Contributory Causes of Malnutritional Oedema.

a. Microorganisms.

From time to time it has been contended that malnutritional oedema must be due to microbic infection, but the dietetic causation of the disease is so obvious that such theories have never secured wide acceptance.

Jürgens [506] considers that malnutritional oedema is directly or indirectly due to infection. He holds that the ill-balanced diet gives rise to gastro-intestinal disorders, and that microorganisms may then invade the tissues, or may produce toxins which are absorbed from the alimentary tract and thus injure the tissues so as to give rise to oedema.

Writing in 1917, Nocht,[637] in view of the then state of the complettin doctrine, left the question open whether ship beriberi was the outcome of a special form of malnutrition, or of an intoxication by damaged nutrients or by other poisons, or of some form of autointoxication. Wuth [880] considers that the cause must be a true toxin, quite distinct from haemotoxin, and characterised by marked lecithinophilia. Smith [479] in like manner assumes autointoxication to be the direct cause of glaucoma, a local oedema.

b. Inadequate Supply of Energy.

Most authorities on diet are prone to regard a deficient supply of calories, and the consequent disintegration of the

bodily tissues, as the main cause of malnutritional oedema.[684, 902, 1217] We have seen, however, that malnutritional oedema may arise in persons whose diet has a fully adequate calorie content, and we are therefore forced to conclude that calorie deficiency can at most be an accessory factor, one which may predispose to the disease and may reinforce the noxious influence of the main factor. A general deficiency of nutrition has been assigned as the cause.[639, 912, 913] But by parity of reasoning this can be no more than an accessory factor. Absolute starvation does not cause oedema. Some authorities refer to protein insufficiency [1086] or inadequacy [784, 902] as the main cause, but others contest this view.[1078, 1196] One authority considers that an insufficient supply of carbohydrates is the main dietetic defect,[1061] whilst others speak of an excess of carbohydrates as responsible.[902] Bürger, [1217] who believes an insufficiency of calories to be the main cause, thinks also that an ill-balanced diet containing an excess of carbohydrates may favour the onset of malnutritional oedema by its tendency to promote the retention of water. [The carbohydrates are not stored up in the body, and therefore cannot promote the retention of water in the tissues; on the contrary, it has often been possible to detect the presence of hypoglycaemia in this disease.] Whereas Maase and Zondek [1064] regard a lack of fat as the essential cause of the disease, Jansen [1061] reports that although the supply of fat was sometimes insufficient, it was in general adequate. Bigland [1037] speaks in general terms of an insufficient and ill-balanced diet, without saying precisely in what way the food was defective. Knack and Neumann [639] lay the blame upon the excessive ingestion of fluids by persons taking an ill-balanced diet. Kohman [1086] and Nixon [1258] advocate the same theory, without troubling to reflect how innumerable are the persons who consume vast quantities of water or other fluids without being troubled with oedema, provided only that the kidneys are healthy. Denton and Kohman [784] are inclined to regard a lack of calcium in the diet as a possible contributory cause.

c. Complettin Deficiency.

Most investigators, as I have already said, incline to exclude a deficiency of accessory food factors as a cause of

malnutritional oedema.[639, 902, 913, 1064, 1225, 1258] It would seem, however, that a lack of real knowledge of the accessory food factors has led many of these authorities astray, for it is plain that in a number of instances they are thinking only of Funk's vitamin. Sometimes a contention has been put forward which is in manifest conflict with the data reported by the assertor himself. For example, Bürger[902] rejects the theory that a lack of " vitamins " can have caused the disease when the diet consisted of bread, pickled meat, salted meat, lard, kohlrabi (which had obviously been boiled in the usual manner), and a little potato—this being a regimen practically devoid of all accessory food factors! Kohman[1086] will not hear of a lack of A as a cause, finding that to supplement the diet with an abundance of butter makes matters worse, whereas an abundant supplement of B does not increase the dropsy. McCarrison,[1240] on the other hand, insists that butter contains a substance which has an antidropsical effect, and finds that the richness of butter in this substance runs parallel with its richness in A. Elsewhere McCarrison[1056] states that the lack of B in the diet is momentous; it almost always leads to gastro-intestinal disorders, to dysentery and diarrhoea, which culminate in oedema. In another publication, Bürger points out that in the diet which induces malnutritional oedema the quantity of complettin is usually very small, and may be further reduced by various methods of preparation (excessive or unduly prolonged heating, the pouring away of the water in which the food has been boiled); consequently, we must not reject the possibility that an insufficiency of " vitamins " in the food may be an etiological factor. When Schlesinger[1165] refers to neuritis as a complication, and when Nocht refers to scurvy as a complication, it is obvious that there must have been a lack of complettins to produce these intercurrent disorders, and that such a lack may therefore have had something to do with inducing the malnutritional oedema as well. Zambrzycki[1162] regards malnutritional oedema, scurvy, and beriberi as nutritive disorders which have a kindred etiology. He says that the same symptoms are common to all three diseases, the difference being the extent to which this or that symptom predominates. In beriberi the pareses are most conspicuous; in scurvy, the

symptoms of the haemorrhagic diatheses give the specific character to the disease; and the most notable feature of malnutritional oedema is, of course, the anasarca.

d. Malnutritional Oedema akin to Mehlnährschaden.

Many authorities draw attention to the resemblances between malnutritional oedema and Mehlnährschaden; among them I may mention Bürger,[902] Schittenhelm and Schlecht,[913] and Maver.[1225] This is in conformity with the foregoing, inasmuch as a lack of complettins plays its part in the causation of Mehlnährschaden. Funk [388] has definitely classed Mehlnährschaden among the avitaminoses, using the latter term in the wider significance in which it is still current to-day (as equivalent to acomplettinoses). But in the review of Funk's work in the "Zentralblatt für Biochemie und Biophysik" (1914, 16, 758), the reviewer, who is a medical practitioner, is strongly opposed to the idea that Mehlnährschaden, Milchnährschaden, rickets, and spasmophilia are to be regarded as deficiency diseases.

There are certain respects in which Mehlnährschaden is definitely distinguished from malnutritional oedema. First of all, whereas in malnutritional oedema there is a great relaxation of muscular tone, in Mehlnährschaden the muscles are from the first hard and hypertonic. Furthermore, in Mehlnährschaden there is marked nervous irritability which manifests itself in the proneness to muscular spasm, and perhaps assimilates the disease to spasmophilia rather than to malnutritional oedema. For in malnutritional oedema there are no nervous symptoms except for the occasional paraesthesias, and even these are probably a secondary outcome of the mechanical pressure exercised by the swollen tissues on the nerves. It is no more than a chance resemblance that, in the long run, atrophy and oedema may become associated in both diseases.

7. Causes of Dropsy.

a. Chemical Causes.

Obviously, by the routes hitherto followed there is no hope of reaching a clear conception of the etiology of the

disease. We shall do better to set out from a study of the morbid anatomy, and to enquire how, in the given cases, the oedematogenic diet can have induced this. What we have to consider is not any mechanical lesion of the capillaries, for that would lead to a haemorrhagic and not to a merely serous infiltration of the tissues. We are concerned with a chemical lesion of the capillary walls, and with an interference with the flow of blood through the venous system. Such an interference, for instance, as results from a great lowering of blood-pressure, causing passive congestion. We have also to think of a true hydraemia, a decline in the internal pressure of the serum, dependent upon its excessive dilution, leading to a so-called dyscrasic oedema of a general character—to anasarca.

b. Cholesterin Impoverishment.

A chemical injury of the capillary walls, just as in the case of the walls of the larger bloodvessels, may arise in either of two chief ways. The first of these is by a disappearance of the lipoids from the cellular walls, which makes them more permeable by watery solutions. Such changes ensue when, in especial, any of the cholesterin compounds are lacking in the cells of the capillary wall, either because there is a general impoverishment of the blood in respect of these compounds, or else because the solubility of the compounds in blood-serum is increased.

Such a disappearance of the cholesterin esters is especially noted in diseases in which, in conjunction with a hindrance to the new formation of such esters, there is a hypertrophy of certain organs very rich in these compounds—notably the adrenals. In the deficiency diseases in general, and in malnutritional oedema in particular, there is such a hypertrophy of the adrenals. More particularly we know that in malnutritional oedema this hypertrophy is attended by a fatty degeneration of the adrenals, which means that these organs are overloaded with cholesterin esters. That change alone, however, cannot give rise to impoverishment of the blood. There must simultaneously be some interference with a new formation of the cholesterin esters in the blood. But we have no evidence of anything of the kind in malnutritional oedema, for the oedematogenic diet has usually contained

an ample supply both of free cholesterins and of cholesterin esters. Moreover, Albrecht and Weltmann (" Wiener klinische Wochenschrift," 1911, No. 14) have proved that in most cases, when the cholesterin content of the blood declines—as it will tend to decline from time to time when this substance is deficient in the food—the adrenals readily surrender part of their store of cholesterin esters.

A second way of inducing cholesterin impoverishment of the capillary walls might be that there should be an accumulation of lipoid-solvent materials in the blood; but in that case there would not be a deficiency of cholesterin compounds in the blood itself, such as we find in malnutritional oedema; there would rather be an excess of cholesterins, such as is known to occur in dogs during ether anaesthesia. (Cf. Bang.[508]) It follows, therefore, that the before-mentioned occurrence of acetone in the blood can have nothing to do with the question we are considering, although acetone is a lipoid-solvent.

Much more important is another consideration, a fact which has again and again been demonstrated. The ratio between cholesterin compounds and neutral fat in the blood is remarkably constant. If for any reason the richness of the blood in neutral fats should decline, there is also noted a decline in the amount of cholesterin bodies in the blood; and when the proportion of the one class of substances in the blood increases, the proportion of the other class increases also. This might explain why the blood is poor in cholesterin when the diet contains too little fat. But since, as far as malnutritional oedema is concerned, the oedematogenic diet has often been shown to contain an abundance of fat, we cannot look upon this cause, either, as accounting, in general, for the cholesterin impoverishment of the blood, and thus indirectly for the origin of the oedema.

There is, however, a persistent factor in the clinical picture, one which might lead to a lack of fat, and consequently to a lack of cholesterin, in the blood. We have already seen that in malnutritional oedema the digestive glands do their work badly, so that sometimes there may be more or less complete achylia. This will make it impossible for the absorption of fat and cholesterins from the intestine to be effective,

and thus the known impoverishment of the blood in fat and cholesterin compounds is easily explicable as a result of the disorder of digestion. But since the blood still retains its power of dissolving the cholesterin compounds, it will dissolve them out of the vascular walls (and they will then be withdrawn from the blood for storage in the morbidly hypertrophied adrenals). This mechanism may account for the onset of general oedema.

But the factor we have just been considering can only come into operation in the later stages of the disease. When such an impoverishment in cholesterin bodies gets to work as a cause of oedema, it must promptly induce universal anasarca. We have learned, however, that the oedema comes on gradually, beginning in the feet and ankles, and extending upwards by degrees. Not until the final stages does universal anasarca ensue.

c. Anomalies of inorganic Metabolism

A second way in which a chemical lesion of the capillary walls may arise is through the instrumentality of the metabolism of the inorganic salts. Here we have three possibilities to consider. First the blood may be relatively or absolutely overloaded with sodium ions ; and secondly it may be impoverished in respect of calcium ions, for this impoverishment would have a similar effect. In both cases there may ensue a transudation of serum from the blood into the tissues ; whereas, conversely, when the blood is comparatively poor in sodium ions, or fully supplied with calcium ions, serum will tend to pass out of the tissues through the vascular walls into the capillaries. To understand this we have to remember that, even under perfectly normal physiological conditions, fluid is continually passing from the blood into the tissues and from the tissues into the blood. This transudation, however, is not a filtration ; nor is it, mainly at any rate, the result of osmosis. It is due to secretory activities on the part of the vascular endothelium, which, both from the blood and from the tissues, incorporates substances in solution, and then selectively passes them on to one side or the other. This endothelial activity is paralysed by an excess of sodium ions, and on the other hand it is stimulated by a sufficiency

of calcium ions. Oedema can be induced by an excessive supply of sodium ions; and, conversely, absorption from dropsical tissues can be promoted by the supply of calcium ions. (I should mention that the absorption of dropsical effusion from the body cavities is not furthered by the supply of calcium, which has an unfavourable effect here).

But there is a third way in which variations in the metabolism of inorganic salts may injuriously affect the vascular system. We know that the effect of acids on the walls of the bloodvessels is to induce swelling and hyaline degeneration. Even free carbonic acid may have this action. Now, the oedematogenic diet always contains an excess of inorganic acids, so that there must be acidosis in malnutritional oedema. Moreover, the increase of ammonia and acetone in the blood and the urine of these patients is a definite indication of acidosis.

d. Effect of Hydraemia.

We have, then, found an effective cause for the occurrence of dropsy in malnutritional oedema, but we have to make the same reserve that we made in the case of cholesterin impoverishment. This disturbance of the metabolism of inorganic salts would necessarily lead to general anasarca, such as does in fact arise during the final stages of the disease. It follows, therefore, that cholesterin impoverishment and disorder of inorganic metabolism can be no more than contributory causes. What we are still in search of is some predisposing cause, which can account for the localisation of the initial oedema. But before we pursue this question, we have to consider a third factor, which may very well explain the onset of the oedema, but itself in turn requires to be explained. I refer to the condition of hydraemia which is actually proved to exist—the general impoverishment of the blood as regards solid constituents, and the undue richness of the blood in water. Excessive wateriness of the blood must of course tend to result, by osmosis, in the passage of fluid into the tissues, especially if there should be a lowering of the osmotic pressure of the blood. This latter change is not, however, associated; for in malnutritional oedema, thanks to the accumulation of sodium chloride in the blood, the osmotic pressure is kept at its normal level—and in all the cases he

has investigated, Feigl [716] has found the cryoscopic conditions normal. Of course this means no more than that the relative sodium-chloride content of the dropsical effusion is normal. The impoverishment of the blood in respect of certain other ingredients involves a reduction of the partial pressure of these substances, which must lead to an impairment of the proper relationship between the blood and the tissue fluid. In consequence of this, a transudation of serum will ensue until the partial pressure of these substances in the tissues has become identical with that in the blood.

This explanation may seem most acceptable, but in reality it merely thrusts back the problem a stage further, for we have to ask, What is the cause of the hydraemia? Although many authorities tell us that the wateriness of the regimen is the cause, this is absurd. Provided my organism is healthy, it makes no difference if I consume a lot of watery nutriment, or even drink large quantities of pure water. The body has its own way of dealing with an excess of water. The cardinal point of which we are in search is the explanation of the failure of this regulative mechanism.

e. Cardiac Asthenia.

The regulative capacity of the organism in this respect can, first of all, be reduced by cardiac asthenia. But though all authorities refer to the existence of bradycardia in the acute stage of the disease, this is by no means synonymous with cardiac asthenia, and is probably a consequence rather than a cause of the increase in the quantity of the blood and of the fall of the blood-pressure. Furthermore, although the lowering of the blood-pressure may lead to a reduction in renal excretion, it can hardly account for the hydraemia. We must, therefore, direct our attention in the first place to the organs preeminently responsible for excretion, namely the kidneys; we must enquire whether, in the pathogenic diet, there are any factors competent to interfere with the process of renal excretion.

f. Behaviour of the Kidneys.

In this connexion, once more, we have three symptoms already known to us to reckon with—symptoms which are

somewhat conflicting, so that a satisfactory solution of the problem is rather difficult. First of all there is the hydraemia; secondly, the polyuria; and, thirdly, the nycturia. It is difficult to understand how hydraemia can arise when there is polyuria, and when the polyuria is so marked as to lead to nycturia.

Polyuria is a familiar symptom in persons who consume a diet containing large quantities of water and also substances containing an abundance of inorganic salts, especially calcium and potassium salts. It has been my experience that in persons who have hitherto been little accustomed to a vegetarian diet, and who therefore, when they consume considerable quantities of vegetable food, are prone to season it strongly with salt, there is apt to be delayed excretion, so that they are forced to rise several times during the night in order to pass water. In proportion as the sodium chloride is eliminated from the body, the nocturnal diuresis declines, and, on the other hand, the flow of urine during the daytime increases. In a healthy individual who consumes only moderate quantities of table salt (not more than 7 grammes daily) the kidneys act so promptly that after a liberal helping of watery vegetables, such as asparagus, young green peas, kohlrabi, or carrots, the desire to pass water becomes urgent within ten minutes.

g. The Effect of the various Ions on the Kidneys.

The hindrance to the natural excretion of water must therefore depend on the effect of the sodium ion on the renal tissue. This effect is reinforced by the simultaneous presence of the chlorine ion, which likewise hinders the activity of the kidneys. A deficient supply of calcium contributes to the retardation. In physiologically healthy conditions, calcium and sodium have contrary actions on the renal functions. Calcium, by its effect on nerve and muscle, reinforces the stimulating influence of the potassium ion. Sodium and chlorine tend to paralyse renal activity; potassium stimulates and calcium regulates this activity.

In the oedematogenic diet, there is an excess of sodium and chlorine, in conjunction with a lack of calcium, and frequently with a lack of potassium. These conditions impair the excretory activity of the kidneys, and simultaneously

tend to paralyse the sphincter vesicae. Consequently, an urgent desire to make water is felt even when there is but a very small quantity of fluid in the bladder. It is a fact that these patients all complain of a frequent desire to pass water, although they pass only small quantities at a time (from 50 to 150 cc.). Nevertheless, as Röse's researches and mine have shown, despite the paralysing effect of the sodium ion on renal activity, the consumption of large quantities of sodium in the form of table salt (more than 12 grammes) induces marked diuresis. To understand this phenomenon, we must remember that in the excretory function of the kidneys two distinct factors are at work. The genuinely regulative function of these organs depends upon a selective excretion; the kidneys are excretory glands, and it is, primarily, this excretory activity which is affected by small quantities of ions. But in addition, the kidney tissue, like that of all other organs, is subject to the laws of osmotic pressure; there must be an osmotic equilibrium between excretion by the kidneys and the constitution of the blood. It is to this osmotic element in the renal function that we must refer the increase in the urinary excretion when large quantities of common salt are consumed. The bodily tissues are adapted for a specific osmotic pressure, and as soon as this pressure is exceeded, the ion whose partial pressure is excessive is automatically excreted by the kidneys. But since, in this process, the genuinely active function of the kidneys plays no part, it follows that, as far as the excretion of other substances is concerned, excretion takes place only in proportion as the blood passing through the kidneys is able to provide the actively excreting tissues of these organs with a sufficiency of the stimulating and regulating ions.

We have already learned that the excretion of sodium chloride in the urine is always a tardy process, and the facts just mentioned explain the retardation. They also enable us to understand that a sufficient excess of water and sodium chloride may ultimately lead to polyuria although at the same time the blood has become hydraemic. The secretory activity of the kidneys has been to a considerable extent paralysed, and nevertheless the excessive supply of sodium chloride has raised the osmotic pressure of this salt so high

as to promote diuresis. If the accumulation of water and sodium chloride in the body be considerable, the diuresis may be excessive, and may be none the less inadequate to free the blood from its excess of water.

h. The Reduction of Blood-Pressure.

A third factor has now to be considered, one competent unaided to induce oedema. In my account of the polyneuritic disorders I referred to McCarrison's hypothesis that the hypertrophy of the adrenals led to an increased formation of adrenalin, and that the resulting constriction of the capillaries caused an exudation of serum into the tissues. I quoted Barr, however, in support of the contention that adrenalin acts on the larger bloodvessels rather than on the arterioles, so that a surplus production of adrenalin must favour the circulation and must tend to counteract the occurrence of oedema. But in beriberi, notwithstanding the hypertrophy of the adrenals, the blood-pressure is low, and this leads to so great a flow of blood through the arteries that the outflow from the capillaries is insufficient. In view of these considerations, McCarrison has formally withdrawn his hypothesis. In malnutritional oedema, the fall in blood-pressure, the relaxation of the great vessels, is even more marked than in beriberi, so that on this count alone we should expect the onset of oedema.

i. The Effect of B Deficiency.

But what is the cause of the fall in blood-pressure ? There are two factors, which work hand in hand. When studying the determinants of growth we found that vegetable extracts rich in B could induce a lowering of blood-pressure. But this factor is not in question here, for in malnutritional oedema there is a lack of B in the diet, not an excess. However, the deficiency of B may be the indirect cause, for it may act by impairing the secretory activities of the endocrine glands. In the case of the polyneuritic disorders we saw that this applies to the production of adrenalin, for although the adrenals are hypertrophied in these disorders, they do not supply a normal quantity of adrenalin.

k. The Lack of Potassium and Calcium.

The lack of B, however, cannot make itself felt quickly. There must be a considerable period of incubation before the insufficiencies arising from this lack can induce oedema. But simultaneously with the B deficiency there is at work a second factor competent to bring about a relaxation of the bloodvessels. I have already shown that an excess of sodium and chlorine ions in conjunction with a deficiency of potassium and calcium tends to paralyse the vital secretory activities of the endothelial cells lining the bloodvessels, with the result that the interchange between the blood and the tissues is predominantly effected by differences in osmotic pressure instead of by the active intervention of the vascular endothelium. But the richness of the blood in these various ions has another direct influence upon the bloodvessels, upon the arterial walls this time. Just as in the case of the sphincter vescicae, the intestinal musculature, and the ureter, an excess of sodium and chlorine ions has a paralysing influence upon the involuntary muscular fibres in the arterial walls. This action is reinforced by the lack of the corrective influence of the calcium and potassium ions. Consequently, the excess of sodium chloride and the deficiency of calcium and potassium in the blood must lead to a relaxation of the arterial musculature, and this will obviously induce a fall in blood-pressure.

8. Summary.

Let us now summarise the foregoing considerations. We may regard as the primary cause of the oedema the decline in the secretory activity of the kidneys owing to the lack of calcium and potassium. Consequently the blood becomes hydraemic. The transudation of the hydraemic serum into the tissues is brought about by a paralysis of the regulative activity of the vascular endothelium owing to the calcium and potassium activity; also by the hydraemia; also by the relaxation of the bloodvessels consequent on the lack of calcium and potassium, which leads to passive congestion, and by other chemical changes in the blood and the vascular walls. The passive oedema must make its appearance first where the driving power of the heart has the greatest difficulties

in making itself felt—in the lower extremities, and notably in the joints, where the circulation is especially sluggish. The tendency to oedema is reinforced by the failure of the adrenals to provide a sufficiency of adrenalin.

All these factors are brought into play for much the same reason. The lack of B in the diet, which leads to a decline in glandular activity, is responsible for the failure of the adrenals and for the consequent loss of arterial tone. The deficiency of lipoids in the vascular walls and the blood is referable to the defective absorption of lipoids from the intestinal tract, and this, too, is an outcome of B deficiency. A further change in the vascular walls and in the blood is due to the excessive consumption of table salt, and to the lack of calcium and perhaps of potassium ions. The degeneration of the walls of the bloodvessels is accentuated by the acidosis consequent on the diet. Furthermore, the acidosis and the other effects of inorganic metabolism have a directly paralysing influence upon the arterial musculature, and also upon the secretory activity of the kidneys; while the large quantities of sodium chloride, raising the osmotic pressure of this salt, induces a morbid diuresis, which nevertheless does not suffice to clear the surplus water out of the system.

A study of the actual diet should, therefore, enable us to ascertain the factors leading to oedema. There must be a lack of B, a lack of calcium, and perhaps a lack of potassium, in conjunction with an excess of sodium chloride, together with an abundant consumption of fluid. It is possible that a lack of A may be contributory, for according to McCarrison [1240] this complettin is able to hinder the onset of oedema. But McCarrison's observation has not yet been confirmed.

O. Bossert [1014] reports a very interesting case bearing upon these theories. In children affected with spasmophilia upon a gruel diet, a raw egg was added to make the diet better balanced. The consequence was the onset of oedema, mainly in the feet and legs, but also to some extent in the face, and occasionally carpopedal spasms were noted. The symptoms promptly disappeared when the eggs were discontinued. While the oedema was present, Bossert found that there was marked retention of nitrogen and inorganic salts; with the withdrawal of the eggs, and concurrently with the disappear-

ance of the oedema, the retained substances were excreted. Bossert considers that local changes in the tissues with a relative lack of calcium in the interstitial fluid of the tissues, leading to an accumulation of chlorine and alkali in this fluid, must have been the cause of the trouble. Now the calcium impoverishment preexisted, and since there is an abundance of calcium in yolk of egg, the giving of the eggs ought to have had a good effect as far as this matter was concerned. But, together with the calcium, there was introduced by the addition to the diet a marked excess of sulphuric acid and still more of phosphoric acid, so that despite the absolute enrichment with calcium there must have been an increase in the relative impoverishment as far as this ion was concerned. Furthermore, the acidosis already due to the gruel diet must have been accentuated. In these cases, however, there was a factor at work which is not operative in ordinary malnutritional oedema. Eggs are very rich in lecithins; during the decomposition of lecithins in the processes of digestion or in the blood, cholin is liberated, and this natural antagonist of adrenalin must give rise to a lowering of blood-pressure. Even though the conditions for the onset of oedema already existed, they did not become fully operative until a condition of passive congestion was brought about by the action of the cholin. A contributory, and perhaps decisive, influence was exercised by the deficiency of nervous tone in these spasmophiliac children, and this perhaps explains why the symptoms were noted in spasmophiliac patients only.

Pending fuller knowledge, we may therefore regard a lack of B, of calcium, and sometimes of potassium and A as well, in conjunction with an excess of sodium chloride, inorganic acids, and water, as the determinants of malnutritional oedema.

Addendum to Chapter Eight: Kindred nutritive Disorders.

a. Mehlnährschaden.

We have already learned that various authorities [902, 913, 1225] consider that there is a kinship between the Mehlnährschaden of infants-in-arms and malnutritional oedema. It will therefore be expedient to undertake a more detailed examination of the factors that may contribute to the onset of Mehlnährschaden.

It has been shown that at the very outset this disease is distinguished from malnutritional oedema inasmuch as in the latter the muscles are relaxed and toneless, whereas in Mehlnährschaden they are hard and hypertonic. Furthermore, in malnutritional oedema there are no nervous symptoms (unless polyneuritis be present as a complication), whereas in Mehlnährschaden there is a nervous hyperirritability which may lead to tetanoid spasms. Again at an early stage of Mehlnährschaden, the little patients suffer from moderate meteorism. By degrees, the nutritive condition grows worse, until ultimately a markedly atrophic state arises. In the last stages, there may be oedema. To complete the picture, it is necessary to add that acute gastro-intestinal disorder is a frequent complication. There is also a notable increase in the susceptibility to every kind of infection.

The diet in these cases has consisted mainly of gruel, mush, or porridge of some kind, to which sugar and fat are often added to promote energy. The errors of such a diet from the standpoint of modern dietetics are obvious. We have learned that all the cereals have certain defects which may be looked upon as characteristic of these nutrients. As regards inorganic salts, they are deficient in sodium and calcium ; they are also poorly supplied with organically combined sulphur and with bases generally ; but they contain a superabundance of inorganic acid-formers and of potassium. The cereals are also poor in B, A, and C, the poverty being more marked in proportion to the fineness of the flour. Finally, the proteins of the cereals are always inadequate ; they are lacking to some extent in the ringed amino-acids, and are especially poor in lysin and cystin. These defects afford a ready explanation of the causation of the disease. The deficiency of A and B impairs the activity of the digestive glands, so that the utilisation of a diet that is already inadequate is rendered incomplete, and at the same time the door is opened for all kinds of intestinal infections and fermentations. The excess of potassium, when there is a deficiency of sodium as an antagoniser and of calcium as a corrective, leads to muscular hypertension, to contractures ; and at the same time induces a nervous hyperexcitability which manifests itself in tetanoid spasms. In most cases the lack of A in the gruel is fairly

well compensated by the addition of butter. When this supplement is lacking (as in Denmark, where the butter is destined for export) xerophthalmia often occurs as a complication. This is supposed to be the chief cause of blindness among Danish children.[940]

The lack of complettins and of important inorganic nutrients, the acidosis, and in especial the lack of an adequate protein, must gradually induce general atrophy, as the outcome of which the glands will be paralysed and atrophied, and more particularly the production of adrenalin will be reduced.[1240] In the long run there will ensue a fall in blood-pressure, and this, in conjunction with the onset of cardiac asthenia due to the malnutrition and the lack of calcium, will give rise to oedema.

b. Milchnährschaden.

Aron [388] protests against confounding Mehlnährschaden with Milchnährschaden, probably with justice. Milchnährschaden, which is a rarer disease than Mehlnährschaden, is a result of the hand feeding of infants with milk, especially cow's milk. Ordinarily, in this form of artificial feeding, the milk is greatly diluted and is also pasteurised or at least scalded. The first symptom of the disorder is that sleep is greatly disturbed; the infant is overtired, and manifests its discomfort by repeated fits of crying. The skin becomes pale and turgid, and is morbidly sensitive to injury. The tonicity of the tissues and the blood-pressure decline; the stools contain large quantities of fatty soaps; and there is marked meteorism. For a time there is an arrest of weight, and then the weight actually falls until extreme atrophy has been established. Marked intolerance of fat is displayed, especially when cream is added to the milk in the hope of improving the nutritive condition.

Nervous symptoms have not been noted, but the disease may sometimes be complicated with infantile scurvy.

c. Fat as a noxious Factor in Infant Feeding.

The fatty acids of the milk have hitherto been regarded as responsible for Milchnährschaden. It has been supposed that, as the outcome of some gastro-intestinal disturbance,

the unabsorbed fatty acids have been eliminated in the stools as sodium, potassium, or calcium soaps, this leading to an impoverishment of the body in respect of bases.

Czerny considers that the volatile fatty acids in the milk fat are especially to blame, and therefore he and Kleinschmidt recommend the well-known butter-and-flour preparation, made by heating butter with flour so that the volatile fatty acids are driven off. Reiche,[1130] however, reports that children do not thrive permanently on this butter-flour diet, and that ultimately the increase of weight is arrested.

While we may admit that a failure in the absorption of fat may actually lead to the onset of acidosis, the symptom complex of Milchnährschaden cannot be thus explained. But the knowledge we have now acquired concerning the physiology of nutrition should enable us without much difficulty to ascertain the true pathogenic factors in this instance also. In contradistinction to Mehlnährschaden, the dominant feature is here an impoverishment in potassium, and, thanks to the dilution of the milk, also in sodium and calcium, and in bases and inorganic nutrients generally. The deficiency suffices to induce acidosis, and that condition can certainly be aggravated by the losses due to the fatty discharge in the stools. But the acidosis does not suffice to explain the symptoms, even though the impoverishment in respect of inorganic nutrients must certainly tend to reduce the vigour of the vital reactions.

The pallor, the turgidity of the skin, the digestive disorders, the loss of tonicity of the tissues, the sensitiveness of the skin to injury, the weakness of the digestion, and the increased susceptibility to infections, comprise a syndrome we have already noted when discussing the conditions of growth, and we have recognised it to be an outcome of B deficiency. I have pointed out that the B content of cow's milk is primarily low, and that therefore a dilution of cow's milk must make the danger of B deficiency acute.

It is, of course, obvious that when there is a general lack of inorganic nutrients together with acidosis and defective power to digest fats, the symptoms of the disease can only be aggravated by increasing the amount of fat in the milk through the addition of cream.

CHAPTER NINE

PELLAGRA

1. Clinical Picture.

Those who speak to-day of the avitaminoses, or, as I prefer to call them, of the acomplettinoses, have usually three diseases in mind: scurvy, beriberi, and pellagra. A full account has been given of beriberi and scurvy, and it remains only to undertake a critical discussion of pellagra. The primary requisite in this connexion is a precise knowledge of the symptom complex that passes by that name. The first specific feature is the chronicity of its course. At the outset there are slight attacks, chiefly in spring and autumn; and during the intervals between these the manifestations recede and may completely disappear. In the attacks, the patient exhibits a peculiar awkwardness of movement, which makes his gait typically cumbrous. He complains of headache, dizziness, sleeplessness, weakness, paraesthesias, and neuralgias. He is listless, depressed, and irritable. Gradually, loss of appetite sets in, sometimes culminating in a positive loathing for his ordinary food, but occasionally alternating with bulimia. The tongue is apt to be thickly coated, or in a state of inflammatory desquamation; there are salivation, heartburn, often intense thirst and gastralgia; in many cases, diarrhoea completes the picture of severe gastro-intestinal disorder. The attacks commonly recur year after year, becoming worse perhaps, but not exhibiting any other change. By degrees, however, upon this basis, there is superimposed the group of serious nervous disturbances typical of advanced pellagra. Concurrently with their onset, in the spring or autumn an eruption usually appears. The digestive troubles become more obstinate, stubborn constipation sometimes

alternating with diarrhoea. Emaciation sets in, and the aspect is now cachectic. Nephritis is common, and the urine (which is often alkaline from secondary infection of the bladder) contains albumin. When there is marked gastro-intestinal disorder, indicanuria is not uncommon. Anaemia, with moderate lymphocytosis, develops as a secondary symptom. Most characteristic of all are paralytic manifestations, often associated with nerve atrophy and with tonic or clonic spasm. The knee-jerks are usually exaggerated, but in some cases are absent; Romberg's symptom is generally present. The gait is that of spastic paraplegia. Vertigo, tremor, and twitching are common; and the spasms may pass on into epileptiform convulsions. Other typical symptoms are photophobia, retinitis, and at times disorder of the auditory nerve. Severe neuralgias and obstinate paraesthesias of the most multiform character contribute to the development of the mental disturbance which often arises at this stage, and may ultimately drive the patient to suicide. The mental symptoms may take the form of melancholia, mania, cyclic insanity, paranoid and obsessive ideas, etc. The apathy and the amnesia may affect the intelligence so profoundly that the mental state comes to simulate that of paralytic dementia.

The parts affected by the exanthem are especially those exposed to light, and notably to direct sunlight. There is a remarkably symmetrical erythema, which may be light-red, dark-red, or bluish in tint. The affected areas are the seats of a burning sensation, which is apt to be almost unbearable at night; and vesicles or pustules often form upon the skin of these regions. This vesicular dermatitis gradually leads to the formation of crusts, or sometimes to the onset of typical eczema. After a number of such attacks of dermatitis, hyperkeratosis sets in, subsequently leading to marked desquamation, after which the skin is left in a dry, raw, parchmenty, and deeply pigmented state. Ultimately, the skin becomes shrunken, wrinkled, and atrophic. Striking as the eruptions are, they are not universal in this disease. Especially in America,[1007] many cases have been seen of unmistakable pellagra without any eruption ("pellagra sine pellagra"); and other cases in which the exanthem has been limited to the formation of scales, or to rhagades in the corners of the mouth.

I have already referred to the fact that the course of pellagra is chronic. In the worst cases, it is true that within a few months or years death may occur from cachexia, or in consequence of the mental or nervous disturbances. As a rule, however, the illness lasts for decades, and in exceptional instances throughout a life of normal duration.

There is, however, an acute form, the so-called typhus pellagrosus, characterised by pyrexia and a typhoid state, and by an accentuation of all the usual symptoms. The intelligence is clouded at an early stage, and before long delirium occurs. In contradistinction to the chronic form of the disease, in the acute form there is a hypertonicity of the whole muscular system, sometimes so marked as to cause opisthotonus. As in severe attacks of typhoid and typhus, the patients are completely helpless, and pass the faeces and urine involuntarily. Death ensues within a week or two, to the accompaniment of grave complications, such as pneumonia, encephalitis, extensive bed-sores, etc. Notwithstanding the onset of this typhoid state, no typical microorganisms have been found in the stools or in the blood in this form of the disease; it is doubtless due only to severe complications in the form of gastro-intestinal disturbances. The amoebae of amoebic dysentery, various microorganisms, nematode worms, etc., have been found in great variety in these cases. We may therefore presume that the typhoid state is the outcome of the association of the severe gastro-intestinal disorder and the malnutrition with the nervous symptoms characteristic of pellagra.

In the early stages of pellagra, a complete change of diet offers the best hope of cure, though by no means a certain hope. Without such a change, and in advanced cases, the prognosis is exceedingly grave.

2. Pathological Anatomy.

The first morbid changes take the form of congestion of the whole intestinal tract, passing on into grave atrophy, and often attended by ulceration of the large intestine. There are also degeneration and atrophy of the muscles, the heart, the liver, the spleen, the kidneys, and the endocrine glands. Whereas in the other deficiency diseases, the adrenals are

hypertrophied, in pellagra these glands are markedly atrophied, and may be reduced to one-tenth of their normal size.[1137, 1187, 1192] Degeneration is especially frequent in the medulla of the adrenals and in the Langerhans' islands of the spleen.

In the later stages, when the nervous and mental symptoms have developed, we find extensive and diversified changes in the nervous system. Most conspicuous are the signs of inflammation in the meninges of the brain and the spinal cord. There is degeneration of the large ganglion cells in the cerebral cortex, of the posterior horns of the spinal cord, and of the ganglia of the posterior roots; less often there is degeneration in the cells of Clarke's columns and in those of the anterior horns. There are also symmetrical degenerative or sclerotic changes in the posterior tracts (especially in the columns of Goll), the pyramidal tracts, the lateral tracts, and above all in the posterior roots. According to Roaf,[1066] the cells of the ganglia of the sympathetic always exhibit a condition of plasmolysis, attended with atrophy of the medullated nerve fibres [1192]—changes which have a great resemblance to those met with in Addison's disease. (Cf. also [1137, 1176].)

As previously mentioned, the glands participate in the general atrophy, and this statement applies especially to the endocrine glands.[1137, 1192] But the first of all the organs to be involved in the atrophic process would seem to be the digestive glands—the salivary glands alone excepted. At the very outset of the disease there is a falling-off in the amount of gastric juice, in the peptolytic power of the secretion, and in its hydrochloric-acid richness. In severe cases, there may be no acid at all. This failure of secretion spreads by degrees to the whole digestive tract, so that in bad cases there is complete achylia.[170, 318, 1187] The inevitable result is a grave disorder of digestion and absorption, this trouble being accentuated by the atrophy of the mucous membranes.[285, 302, 337] As a result, even in the early stages, the nitrogenous balance tends towards the negative,[216, 318] and before long becomes definitely negative.[1187] Except for the interference with absorption, metabolism is said to run a normal course [318]; but this can only be true in very mild cases. Nistico [214] claims that he has observed a falling-off in the tolerance for

carbohydrates, but his conception of the normal tolerance is so high (1·5 to 2·5 grammes of glucose per kilogramme of body-weight) that we are hardly entitled to speak of a real reduction in the carbohydrate tolerance.

The digestive disorders, and especially the lack of hydrochloric acid in the stomach, cannot fail to react unfavourably upon the nature of the intestinal flora, and at an early stage fermentations and putrefactions of all kinds set in. Owing to the failure of the natural powers of resistance of the alimentary tract, every conceivable kind of affection of the stomach and bowel may ensue, ranging from simple heartburn to typhoid. Of course these disorders impair yet further the chances of the patient's being satisfactorily nourished.[273, 285, 337, 1066, 1176, 1187]

There is also grave disturbance in the balance of nutrition as regards inorganic salts. Even allowing for the fact that absorption is so much impaired, there is a negative balance in the case of all the inorganic nutrients as soon as the disease becomes acute.[285]

The excretion of nitrogen, phosphorus, magnesium, calcium, and potassium in the urine is greatly diminished,[185 285, 302] the reduction affecting the phosphates more than the urea, the alkalies more than the calcium, and the calcium more than the magnesium. When there is a sufficient supply of sodium chloride, the excretion of sodium and of chlorine may be normal or even increased.[184] The quantity of ammonia is always increased, both relatively and absolutely [8, 184, 1206]; and as a further sign of acidosis there is an increased excretion of acetone,[8] and also of kreatinin in conjunction with well-marked kreatinuria.[318] There is no urobilin in the urine [214]; but, owing to the great disturbance of intestinal digestion, there is an increased excretion of indican in the urine, often leading to marked indicanuria.[442, 1066] Galmozzi records the remarkable observation that the sulphur in the urine in the form of ester compounds is diminished, a fact which perhaps depends upon the invariable poverty of the pellagrogenic diet in sulphur

At the outset of the disease there is a moderate fall in blood-pressure (to 119 mm. of mercury); but the relaxation of the vascular tone rapidly increases pari passu with the general loss of muscular tone, and when the disease is thoroughly

established the blood-pressure ranges from 92 mm. to as low as 78 mm.[1187]

In the acute stage we find an excess of lymphocytes in the blood, with neutral leucopenia and a falling-off in the number of eosinophil cells,[144] phenomena met with in all essential anaemias. Reports are very variable as regards the serological conditions, and it will be best to defer the discussion of this matter until we come to consider the probable causes of the disease.

3. The pellagrogenic Diet.

The occurrence of pellagra was first recorded in connexion with an ill-balanced diet consisting chiefly of maize. It has been supposed that the appearance of the disease in Europe dates from the time when the cultivation of maize became widespread in Northern Italy, but there is no proof of this assertion.[212] For a long time it was believed that the pathogenic cause must be connected with maize, though it was uncertain whether the influence was a specific property of the maize or was the outcome of a decomposition of the grain. The importance of maize as pathogenic agent was confirmed by the terrible spread of the illness in Rumania, where the annual toll of deaths from this cause became enormous, and where according to Urbeanu [8] the rural population lived almost exclusively on maize (for the amount of other food consumed per head in the course of a year would hardly exceed two kilogrammes.) Urbeanu was able to prove that an ill-balanced maize diet induced pellagra-like diseases in fowls, and this observation was confirmed by Clementi.[529] It was found that other animals became pellagrous on a maize diet. As far as pigs are concerned, the effects of the inadequacy of maize in respect of the inorganic nutrients predominate in the clinical picture, so that pellagroid symptoms are not conspicuous [347]; but dogs,[406] guineapigs,[293, 352, 360] mice, and rats, become affected with pellagra on an ill-balanced maize diet. (Holst,[171] who experimented on guineapigs, regarded the disease induced by a maize diet in these animals as polyneuritic.)

The method of milling seems to have a certain influence. Suarez [489] reports that mice and pigeons, which on a maize

diet become pellagrous, are affected with polyneuritis if fed exclusively upon finely sifted maize flour or upon maize starch (maizena), and that they can be cured by giving them yeast.

The effects of the maize are most pernicious when it is boiled. In the case of rabbits,[127] and in that of white mice,[132] the supplementing of a diet of boiled maize with an abundance of milk does not prevent the onset of the disease, whereas ordinary mice can thrive on a diet of boiled maize and milk. Mice fed on wheaten rolls and milk were not found to display any pellagrous symptoms. (Cf. Horbaczewski [132].)

In the United States, however, pellagra was found to occur, even in its gravest forms, in human beings whose diet had contained no maize at all, or only a little. Most of these patients were able to command an adequate diet, but for one reason or another (generally they were neurasthenics with a fixed idea that certain foods did not suit them) they lived upon an extremely restricted and therefore ill-balanced regimen. As typical of such defective regimens may be mentioned the experimental diet prescribed by Goldberger and Wheeler,[1157] whose subjects were prisoners voluntarily submitting to the experiment. The diet consisted of wheat and maize in the form of fine flour, maize starch, polished rice, and small quantities of vegetables and fat. The subjects of the experiment were put upon light work and received an allowance of "only" 2,500 to 3,500 calories daily, the diet containing 41 to 54 grammes of protein (mainly vegetable), 91 to 134 grammes of fat, and 387 to 513 grammes of carbohydrate. In all the eleven subjects there occurred, in the course of 205 days, loss of weight and general debility. Abdominal pain and headache were frequent; in three there was diarrhoea, and in five there was an increase of the knee-jerks. In the case of six of the subjects, typical cutaneous manifestations appeared towards the close of the fifth month, but the site of these was in most cases anomalous. In two only did the skin eruption begin on the hands and the nape of the neck; in the other cases it began on the scrotum.

Chittenden and Underhill [599] were able to induce typical pellagra in dogs by feeding them on boiled bean flour, wheaten biscuits, and linseed or cottonseed oil. (Cf. also [691].)

4. Views that have hitherto prevailed concerning the Etiology of Pellagra.

a. Microorganisms as the Cause.

It was, of course, believed at one time that infection must be the cause of epidemics of pellagra,[318, 878] but since it was never possible to discover a specific microbe, the opinion was abandoned. Harris [326] claimed to have induced pellagra in monkeys with morbid material from a case of pellagra after the material had been passed through a Berkefeld filter; but subsequent observers, such as Lavinder, Francis, Grimm, and Lorenz,[397] Siler, Garrison, and McNeal,[412] and Bigland,[1137] were unable to secure any evidence of infection by the inoculation of the pellagrous matter or by its administration by mouth. Bass [183] believed himself to have proved the infectious character of the disease because he observed that fowls acquired pellagra when fed upon maize that had been contaminated with the faeces of pellagra patients; but other investigators were able to show that the alleged proof was invalid, seeing that a maize diet will induce pellagra in fowls in the absence of any such contamination.

Babes reports favourable results from the treatment of pellagra with arsenic, and considers that these successes support his view that the disease is dependent upon a protozoal infection.[668, 669] Collodi [117, 118] contests the inference, for he holds that the observed improvement could readily be explained as the outcome of the familiar stimulating and invigorating action of arsenic. Alessandrini [126] considers that a maize diet is merely a predisposing cause. He believes that this diet gives rise to intestinal disorder which prepares the ground for the invasion of the intestine by certain nematode worms belonging to the family of the filaridae, the larvae of which are to be found in the drinking water of regions where pellagra is prevalent. This observation has not been confirmed, and the presence of filaridae in the intestine of pellagrous patients was doubtless an intercurrent affection on all fours with the accidental presence of different sorts of extraneous micro-organisms.

The commission appointed by the United States Government to study the etiology of pellagra [328] was at first inclined

to regard the disease as a specific infection, and this view seemed to be confirmed when it was found that in Spartanburg, South Carolina, a town where pellagra is endemic, there was a notable decline in the number of cases after considerable attention had been paid to sanitary conditions.[514] According to Roberts,[1007] however, this view has now been generally abandoned, and pellagra is supposed to depend upon some sort of deficiency in the diet. Vallardi,[169] Patta,[103] Carletti,[179, 180] and more recently Boyd,[1187] are definitely opposed to the idea that pellagra is of an infective nature, and in especial they reject the notion that a protozoon is the exciting cause.

The principal idea of the Italian school was that the cause of pellagra must be some sort of deterioration of the maize used for food. In Germany, the view gained strength from the statement of M. Otto that the growth on maize of Italian cultures of Aspergillus fumigatus formed extremely toxic substances, whereas the German stocks of the same fungus did not do so. The growth of Penicillium glaucum upon maize was also said to produce toxins, and in this case likewise the Italian stocks of the mould were the most venomous. Tiraboschi,[77] too, as a result of these researches and of his own, considered that such differences in the virulence of the moulds explained why pellagra appeared in certain localities and not in others. Tizzoni,[142, 170] again, considered that damaged maize was the cause of pellagra, and claimed that while he had been unable to produce pellagra by feeding monkeys on maize, he had succeeded in causing the disease in these animals by the subcutaneous injection of cultures of organisms isolated from the grain. The filtrate from such cultures was said to produce precipitin reactions with the blood of pellagra patients ; but according to a later publication of this authority,[178] did so only after the bacteria in the culture had been broken up.

Camurri [184] also assumes that moulds form a toxin in maize. In the organism of healthy human beings the influence of this toxin is supposed to be counteracted by antibodies, and the toxin can only take full effect in exhausted or debilitated persons.

According to Volpino, Mariani, Bordoni, and Alpago-Novella,[189, 190] both pellagra patients and healthy persons

react very little or not at all to the administration of aqueous extracts of damaged maize *by mouth.* In twelve out of thirteen pellagra patients, however, the *injection* of 1 or 2 cc. of aqueous extract of damaged maize induced manifestations of disorder of the central nervous system, also a rise of temperature, and general, local, and cutaneous disturbances; whereas in healthy persons the same injection induced nothing more than a non-specific rise of temperature. For healthy human beings and animals, the specific substance was almost non-toxic; it resisted heating to 115° C., and was soluble in water. This "pellagrogenin" was precipitable by alcohol, thus contrasting with other toxins sometimes present in damaged maize, which are hardly soluble in water but are readily soluble in alcohol and ether. But these investigators were unable either with the precipitin reaction, or by the method of deviation of the complement, or by passive anaphylaxis, to demonstrate the existence of specific antibodies in the reacting patients, and they therefore came to the conclusion that the substance was not a true toxin but a poison of some other kind.

Carbon and Cazzamalli [327] claim that by growing Aspergillus fumigatus, a Penicillium, Mucor racemosus, or Trichoderma lignorum, on maize, they made the grain so toxic that ordinary mice fed on it became affected with skin troubles or other signs of a pellagrous illness, whereas the original undamaged maize did not engender any illness in the mice. But this report conflicts with the well-established fact that undamaged maize certainly does cause pellagra in mice. To the toxins produced by the before-mentioned moulds, we can therefore attribute at the most a predisposing influence.

b. The Effect of the colouring Matter of Maize, known as Zeochin.

But before long a substance was discovered in maize which certainly seemed to be responsible for the causation of the skin affections forming part of the pellagra syndrome; this was zeochin, the fluorescent colouring matter of yellow maize. We have already learned that Horbaczewski was able to produce pellagra in white mice by feeding them on yellow maize and milk, whereas the same diet did not produce

the illness in ordinary mice. He supposed that the cause of the disease must be the alcohol-soluble colouring matter, which, like all the fluorescent colouring matters, must, he thought, induce a special sensibility to direct sunlight, and indeed a hypersensibility to light in general. This view seemed to him to be confirmed by the observation that the yellow maize was no longer pathogenic after it had been decolourised, whereas white mice fed on their ordinary diet became pellagrous when this diet was supplemented with the colouring matter, which was, however, innocuous to grey mice and rabbits. At most in ordinary mice, injections of the solution of the colouring matter caused local skin trouble when the skin was exposed to the light. According to Suarez,[489] the substance administered to rabbits in the same way has a similar effect upon these animals, but the feeding of it to ordinary mice has no effect at all. These statements were confirmed by Raubitschek,[153] who also reported that zeochin caused skin trouble only in albinos, and only under the influence of light on the skin. Ummes,[245] in like manner, regarded the fluorescent colouring matter of yellow maize as the cause of the skin troubles. All the mice fed on maize soon succumbed, whether the maize was yellow or white; but only when the yellow maize was given did the animal become affected with erythema. The other symptoms of pellagra were supposed to be due to an alcohol-soluble toxin present in maize.

Plausible as this explanation might seem, good reasons for doubting its validity were soon forthcoming. First of all, it is a familiar fact that albinos in general and white mice in particular are much weaker and less resistant than pigmented animals of the same species. Ummes himself points out that white mice perish from starvation more quickly in the light than in the dark. Furthermore, Rondoni [164] proved that white light is, in general, noxious to white mice; also that a maize diet causes pellagra in mice even in the dark, the animals pining, and suffering from a patchy loss of fur. Rondoni was unable to ascertain that the onset of the disease was hastened by the influence of light. The careful investigations of Hirschfelder [250] showed with considerable probability that the zeochin had nothing to do with the case! The idea had, of course, been that the colouring matter was absorbed

into the blood, and that its fluorescence made the blood more sensitive. Hirschfelder was able to show that although the blood-serum of pellagra patients was certainly fluorescent, the fluorescence was no greater than that of the normal serum of healthy persons, and that the tint was precisely the same in the healthy and in the diseased. Moreover, Urbeanu [8] had proved that white maize, which contains no colouring matter, is much more strongly pellagrogenic than yellow maize.

It is as well to point out that the morbific influence of maize seems to diminish with time. Bezzola [80] noted that maize kept in store for a year had even, after boiling, no ill effect on rats, whether the maize was good or damaged. It is doubtful if this investigator's experiments were carried on for a sufficiently long time, but Nitzescu [406] claims to have definitely proved that new maize is more toxic to dogs than the stored grain.

c. The Effect of the Maize Toxin.

Like Ummes, and simultaneously, Rondoni [244] expressed the opinion that the specific manifestations of pellagra were due to a toxin in maize; but he left undecided the question whether this toxin was originally present in the maize or was not produced in it until the grain had been damaged by fermentation or putrefaction. He inclined to the latter view, finding that an aqueous extract made from damaged maize gave rise, even in healthy persons, to a slight reaction, taking the form of a moderate rise in temperature, of dizziness, and of malaise. Since, further, Rondoni discovered that this reaction was stronger in pellagra patients than in healthy persons, it seemed to him that there could hardly be any doubt as to its specificity. Nevertheless, though Volpino and his collaborators [189, 190] had maintained that the reaction was violent in pellagra patients (having the nature, they said, of anaphylaxis), Rondoni was unable to confirm this observation. He therefore felt it impossible to maintain that the unmistakable hypersensibility to the maize protein was really of etiological importance.

Rondoni's conclusion was sustained by a subsequent research of Volpino's own.[360] Volpino found, indeed, that 90 % of pellagra patients were hypersensitive to the decom-

position products of maize protein, but he found also that 20 % of perfectly healthy persons were no less hypersensitive. Such a reaction can hardly be regarded as specific. It was, moreover, impossible by the injection of the so-called pellagrogenin to induce a passive anaphylaxis in guineapigs, though this would have been essential had the theory been sound. Lui and Baccelli [264] likewise reported that the precipitin reaction was not to be trusted for an early diagnosis, seeing that it was not invariable, though it was usually present in the early stages and in the acute exacerbations of the disease, whether intestinal disorder was present or not. But the sera of perfectly healthy persons would also give a similar reaction at times.

Volpino reported, too, that his pellagrogenin did not induce complement formation or a specific precipitin reaction in the serum of pellagra patients—although he believed that by repeated injections of a 10 % solution he ultimately produced a certain degree of immunity, seeing that the animals thus treated remained longer immune to the harmful consequences of a maize diet. When we recall, however, how much the period of incubation varies according to the internal condition and the outward circumstances of pellagra patients, we shall not be inclined to regard this deduction as of much value.

Other observers considered that the injuriousness of the maize depends upon the digestive disorders it evokes. They said that Behring's extensive researches into the pathology of tuberculosis had shown that when there was intestinal disorder it was possible for undecomposed albumin to pass directly into the circulation. In maize feeding, they supposed that the zein in particular was thus absorbed, and gave rise to hypersensitiveness. Especially they maintained that the blood of pellagra patients contained ferments which decomposed zein, ferments whose existence had been proved by the researches of Nitzescu.[359, 399, 406, 442] But Babes and Jonescu [394] were able to show that Abderhalden's reaction to the zein-decomposing ferments is not invariable in the blood of pellagra patients, and that it is fairly common in the blood of healthy persons if some transient gastro-intestinal disorder happens to facilitate the absorption of undecomposed zein.

Gosio had asserted that the blood-serum of pellagra patients contained a precipitin that acted on maize protein, but Rondoni [158] found that this reaction was not peculiar to pellagra patients. Like Abderhalden's defensive-ferment reaction, it is exhibited by the serum of normal persons, just as in the case of all the other vegetable extracts. Moreover, according to Carletti,[180] neither heteroprecipitins nor maize-precipitins are regularly found in the blood of pellagra patients. The occasional presence of such precipitins will certainly not explain the problems of the etiology of pellagra. The blood of the patients is sometimes hypertoxic for other persons, but it is very doubtful whether there can be much connexion between this and the maize diet.

Similar was the trend of the researches of Lucatello and Carletti,[161] who found that antigens from the spleen and adrenals of pellagra patients sometimes induced complement formation, but that none of the antigens gave a positive reaction with the serum in all cases. The attempts of Volpino and Bordoni [463] to induce active immunity were able in guineapigs to secure no more than a " postponement " of death, and in human beings to bring about " moderate improvement." Volpino's claims that the injection of maize extract in pellagra patients can induce an active immunity, and that in like manner a long continuance of a maize diet ultimately leads to the acquirement of immunity against maize protein, are in such flagrant conflict with generally observed facts, that there must obviously have been some error of experiment or interpretation on Volpino's part.

There is no doubt that zein can make its way through the diseased mucous membrance [359, 394, 406, 742] ; but it has been rendered equally certain by Rondoni's experiments [348] that in pellagra we have no ground for supposing that a hypersensibility to maize protein is the cause of the disease. Raubitschek [263] was also unable to discover any invariable changes in the serological behaviour of the blood in pellagra patients. We must, therefore, seek other causes for the disease.

d. The Inadequacy of Maize Protein.

When the work of American investigators directed attention to the importance of the biological value of protein, its

adequacy or inadequacy, in relation to health and disease, it was supposed that the riddle of pellagra had been solved. The work of Osborne and Mendel,[217] and that of Funk,[323] had made it perfectly clear that zein is inadequate. Albertoni and Tullio [337] devoted special attention to the adequacy of the maize proteins in human diet. They came to the conclusion that maize is more slowly digested than other cereals, and is therefore more prone to give rise to putrefactive phenomena in the alimentary canal; that, generally speaking, maize protein is badly utilised; and that if any accumulation of nitrogen within the body should occur in children on a maize diet, this is not due to nitrogenous tissue growth but to the retention of nitrogenous waste products. They therefore came to the conclusion that the injuriousness of maize diet must depend upon the lack of certain nitrogenous tissue builders in the maize protein. Baglioni [393] likewise found that both zein and gliadin were inadequate, and that any storage of nitrogen that occurred when these were the main proteins in the diet must be due to the retention of waste products, seeing that despite this retention there was a steady loss of weight. Röhmann,[472] and more recently Boyd,[1066] regard the inadequacy of maize protein as the main cause of pellagra, though Boyd is careful to explain that there must be other factors. Nitzescu [442] was led by the researches of Albertoni and Tullio and by those of Baglioni to modify his views in the same direction, coming to believe that pellagra must be partly due to the inadequacy of zein and partly to the absorption of unmodified maize protein. Raubitschek [263] had come to the same conclusion at an earlier date. In like manner, immediately after Osborne's researches were published, Centanni and Galassi [293] accepted the idea that the inadequacy of maize protein must be the main cause of pellagra; the photodynamically activating influence of zeochin was a contributory but quite minor factor.

e. North American Experience.

Whilst a study of Italian conditions had thus enforced the conviction that the main cause of the symptoms of pellagra must be directly or indirectly connected with the food, that pellagra must be due to a maize diet, another turn was being

given to the question by North American experience. I have already mentioned that a commission appointed by the United States Government was at first inclined to believe that pellagra must be an infective disorder, but that this opinion was subsequently abandoned. At the outset, Siler, Garrison, and McNeal [364] insisted that pellagra could not be due solely to a maize diet, and indeed that there seemed to be no necessary connexion between the disease and diet. This view was supported by the investigations of Chittenden and Underhill,[559] who found that dogs quickly became affected with severe pellagra on a diet of boiled bean flour or pea flour, wheaten flour, biscuit, and cottonseed or linseed oil, although the nitrogenous balance was maintained. When the diet was supplemented with meat, a cure ensued if the change had been made early enough. In a critical study of these researches, McCollum and Simmonds [691] pointed out that the pathogenic diet had contained rather low-grade proteins, had been defective in respect of A and B, and had been most unsatisfactory as regards its inorganic ingredients. It was a mistake, they said, to think only of proteins when studying the etiology of this disease ; all the other constituents of the diet must be taken into account. Elsewhere, they drew attention to the importance of the law of the minimum in this connexion. It was impossible, they said, when considering the pathogenic factors, to specify the minimal requirement of any nutrient unless the investigator was aware of the biological value of all the other constituents of the diet.

We need not attach much importance to the statement of Jobling and Petersen,[534] with regard to an epidemic of pellagra in Nashville, Tennessee, that the diet of those affected had usually contained sufficient protein. They give no information concerning the biological value of the protein or concerning the other constituents of the diet. Far more important is Funk's observation [303] that the endosperm of the maize grain, just like polished rice, consists mainly of starch and is extremely poor in other nutrients. Still, the observation has not much bearing upon the problem we are now considering, for in pellagrogenic diets the whole grain of the maize is commonly used, and we have learned above that the pure endosperm induces beriberi, not pellagra.

In Italy it was Bravetta [1102] who first observed the occurrence of pellagra independently of a maize diet. He found that many cases of pellagra originated in Italian lunatic asylums, although the diet was abundant, varied, and contained a sufficiency of proteins and vitamins. He noticed, however, that the patients who became affected with pellagra were always weakly and cachectic; and we know that in asylums, just as among neurasthenics who are not under restraint, an almost maniacal aversion to certain articles of diet is common. In such cases the diet actually consumed may be extremely ill-balanced, although plenty of good food is there for the taking. We may assume with considerable probability that this accounts for the cases observed by Bravetta.

f. Specific Importance of Protein Deficiency.

The earlier views regarding the importance of protein have often tended to interfere with the attainment of definite knowledge of this matter. It is doubtless owing to an exaggerated valuation of protein that Bigland [1137] and Chick and Hume [1108] have come to regard a deficiency of protein as the main cause of pellagra. Chick and Hume, giving a diet otherwise adequate, but in which the protein consisted of maize gluten, were unable to induce any pellagroid symptoms (erythema excepted); more especially, the experimental animals exhibited no sign of the typical nervous disorders. On the other hand, we have just learned that Bravetta noted the onset of pellagra in persons whose diet was apparently well provided with proteins. Goldberger, Wheeler, and Sydenstricker,[1101] studying the domestic economy in North America in households where pellagra occurred and in those where there was no pellagra, could not detect any definite relationship between the incidence of the disease and either the calorie content or the protein content of the diet.

The last-mentioned authorities noted, indeed, that before the outbreak of the disease the diet of the pellagra patients had been poor in products of animal origin, especially in milk products and in eggs. On the other hand the illness occurred indifferently upon diets in which maize, wheat, and ripe pulses were respectively predominant. They therefore inferred that

protein inadequacy must be one of the factors of pellagra. The before-mentioned experiments of Goldberger and Wheeler [1157] on criminals, and the investigations of Boyd [1187] concerning the outbreak of pellagra among the Turkish prisoners of war at El Kantara, have the same bearing. In the El Kantara cases, rest and the supply of high-grade protein had excellent results.

g. Pellagra and Malnutritional Oedema.

Bigland [1037] is inclined to regard pellagra as due to malnutrition, and he assimilates the disease to malnutritional oedema. But Bigland's own observation,[1137] and those of Enright,[1176] upon the German prisoners of war in Egypt who became affected with pellagra, conflict with this theory, for both these authorities expressly declare that there was no malnutrition in the ordinary sense of the term. Conversely, Harris,[1062] who studied the incidence of pellagra in Italy during the war, tells us that although the nutritive conditions were wretched, there was a definite decline in the frequency of this disease.

h. Vitamin Deficiency.

Ruhl,[439] McCollum, Simmonds, and Parsons,[691] and Bravetta,[1102] agree in declaring that, despite the important part played by the nervous symptoms, a lack of Funk's vitamin cannot be the cause of pellagra, seeing that the pathogenic diets have always contained an ample supply of this substance. The difference between vitamin deficiency and pellagra is obvious in any case. In vitamin deficiency, the pareses are the outcome of degenerative changes in the muscles, or perhaps of degeneration in the distal ramifications of the peripheral nerves. In pellagra, on the other hand, the degeneration affects the central nervous system.

i. Complettin Deficiency.

It is, however, often asserted that a lack of other complettins is the cause of pellagra. Nightingale,[368] indeed, holds the mistaken view that pellagra and zeism occur only as the outcome of a diet of hulled maize, and this leads him to suppose that a general complettin deficiency is the cause. McCollum,

Simmonds, and Parsons [691] correct this view by maintaining that, whilst there is no lack of Funk's vitamin, a deficiency of A or of B, or of both (in conjunction with other factors), must be of etiological importance. In another paper,[878] indeed, the same authorities restrict the importance of complettin deficiency yet further, for they say that this deficiency must act by lowering the resistance to infection, and that the main cause must be an infective agent. Goldberger, Wheeler, and Sydenstricker,[1101, 1157] on the other hand, consider that complettin deficiency is a direct cause, although other factors must cooperate for the production of the typical pellagra syndrome. A similar view was expressed by Hopkins [1066] in the oft-quoted discussion of British medical authorities regarding the clinical importance of the complettins (London, 1920).

k. The Effect of inorganic Nutrients.

We have seen that almost all the constituents of our diet have in turn been looked upon as more or less directly responsible for the causation of pellagra. The only dietetic factor still to be considered is that of the inorganic nutrients, and we find that some authorities insist upon their importance in this connexion. The first to pay attention to inorganic metabolism in pellagra, and the only experimentalist who has made systematic researches in that field, was the Rumanian physician Urbeanu.[8] He was, indeed, the first to approach the problems of pellagra by the experimental route; and in his latest publication [525] he has been able to record a large number of protracted experiments on animals, extending in some cases to the fifth or sixth generation. Urbeanu was struck by the fact that maize is very poor in inorganic nutrients; that there is a general lack of bases, but also a lack of phosphorus; and that in this respect white maize is worse equipped than yellow maize. His experiments on dogs, guineapigs, fowls, pigeons, and human beings, invariably showed that white maize was far more dangerous than yellow. Although he does not deny that the lack of phosphorus may have some importance, he considers that the general deficiency of bases must be the main cause of injury. Limitations were imposed upon his researches by the lack of opportunity for

elaborate analyses, and he was therefore chiefly concerned with ascertaining the quantities of potassium provided in the food and dealt with by the metabolic processes—starting from the fact that in vegetable nutrients (and, indeed, in animal nutrients as well) potassium is greatly predominant among the bases of the ash. He found, moreover, that the nutrients which have a curative influence, especially potatoes and green vegetables, are extremely rich in potassium. In his writings, therefore, he refers almost exclusively to potassium among the inorganic nutrients, although he says that potassium is to be taken as representative of the inorganic nutrients in general.

Feeding fowls on an exclusive maize diet, he found that the mere addition of calcium carbonate sufficed to prevent the appearance of pellagrous symptoms. Calcium phosphate was less successful than calcium carbonate ; generally speaking, as far as white maize was concerned, calcium carbonate had to be given as well as the phosphate. This is in conformity with Nicolaidi's observation [285] that, even in healthy persons, on an ill-balanced maize diet the calcium and magnesium balance became negative, whereas the phosphorus balance remained positive.

Although in one of their papers, Goldberger and Wheeler [1157] leave the question open whether an inadequate supply of inorganic nutrients may not be responsible for the etiology of pellagra, in another publication [1101] they definitely commit themselves to the opinion that this lack is of crucial importance. In conformity herewith, Centanni and Galassi [293] found that guineapigs, which in general are extremely sensitive to the injurious effect of maize feeding and of feeding with other grains, throve upon a maize diet adequately supplemented with green fodder.

We have already seen that all the cereals, including maize, have a low excess of bases and a poor calcium content. It would be very remarkable should the law of the minimum fail to be valid where a diet of this grain is concerned.[664]

l. The Effect of Silicic Acid.

Alessandrini and Scala,[312, 338, 356] who also refer the causation of pellagra to the peculiarities of inorganic metabolism,

have a favourite theory in this respect, which is doubtless connected with opinions that have been recorded concerning the origin of goitre. They state that in regions where pellagra is prevalent the drinking water is exceptionally rich in colloidal silicic acid, and they say that they have proof that this excess of silicic acid is the real cause of pellagra, maize feeding being no more than a predisposing cause. They believe that the effect of the silicic acid is reinforced by the effects of calcium chloride [!] and aluminium hydrate. Voegtlin,[398] who has obviously been influenced by Alessandrini and Scala, contends that the aluminium found in many vegetables is one of the factors of the disease. Recently, however, Breest [1271] has definitely established that whereas the ingestion of soluble silicic acid, and still more the ingestion of soluble silicates, may lead to a certain accumulation of silicic acid in the animal organism, colloidal silicic acid is not absorbed, and the animals ingesting it remain perfectly healthy if their diet is otherwise satisfactory. Seeing that Alessandrini and Scala found that the troubles they supposed to be due to silicic acid were perfectly relieved by alkalies or by calcium carbonate, we must suppose that the lesions met with in their researches were local or general effects solely due to the influence of acidity. What they tell us of the morbid anatomy of the affections confirms this theory.

m. Mental Influences.

Finally, it is necessary to point out that in pellagra, as in all other nutritive disorders, the onset of the disease may be greatly influenced by psychical causes.[1007] Homesickness, anxiety, sorrow, anything that causes mental depression, may notably accelerate the appearance of pellagra.

n. Complications.

The association of pellagra and scurvy is fairly common,[171] but an association of pellagra and beriberi has not hitherto been noticed. It must be remembered that the period of incubation of beriberi is brief and that the onset of the illness is acute, whereas typical pellagra has an incubation period lasting several years

5. Summary.

Anyone who wishes to ascertain the cause of a nutritive disorder, must be acquainted with the factors that can effect a cure. A comparison of the remedial diet with the pathogenic diet affords the quickest way of learning what constituents of the latter, whether by excess or by defect, must be held accountable for the various symptoms of the disease. The first thing we have to note is that in pellagra, as in other nutritive disorders, the simple addition of butter to the faulty diet tends to make matters worse rather than better.[1158] Enright [1176] reports that a diet of bread, meat, and eggs is beneficial; but it cannot be said that his results were particularly encouraging, although as he was dealing with prisoners of war most of his cases were of recent origin. Of the 65 cases under his care, only 46·1 % were cured, and 33·8 % improved (with marked increase in weight); but in a freshly developed nutritive disorder one might have expected much better results.

Boyd,[1187] whose experience was also made in Egypt, but among Turkish prisoners of war, considers that, in addition to rest, the supply of a high-grade protein is the most important remedial measure. The provision of protein of high biological value and the simultaneous suspension of work, led to a sudden fall in the number of cases reported.

As soon as the inadequacy of the protein in the pathogenic diet had been recognised, as a matter of course the improvement of the quality of the protein was seen to be the first essential for the remedial diet. McCollum, Simmonds, and Parsons [878] report that milk and milk products form the best supplements to a faulty diet. Roberts,[1007] in like manner, demands that the diet shall contain lean meat, eggs, butter, and milk. Apart from Urbeanu, Roberts seems to have been the only authority to stress the great value, in addition, of vegetables rich in bases (this implying the avoidance of ripe pulses!). He informs us that in the United States, where during the last twenty years there have been about half a million cases of pellagra with a mortality of 10 %, the number and the severity of the attacks has notably declined since defective nutrition has been recognised to be the main cause

of the disease. In former days, the largest proportion of the deaths registered as due to pellagra were in cases of typhus pellagrosus; this acute form of the disease is now rare; on the other hand there has been a notable increase in the proportion of slight cases. These lesser cases are apt to be overlooked, especially when there is no dermatitis ("pellagra sine pellagra").

Nevertheless it must not be forgotten that the inadequacy of the protein in the pathogenic diet can by no means account for all the features of the pellagra syndrome. Innumerable experiments upon feeding with an inadequate protein have been made, especially by the American school. Some of these have been carried out for several generations of the experimental animals, and as long as the diet has been in other respects adequate, no disease resembling pellagra has ever been induced. The results of protein inadequacy are: arrest of weight or loss of weight, refusal of food, cachexia, and death from cardiac asthenia—unless, in the debilitated animal, some complication arises to hasten the end. Although the symptoms named are well marked in pellagra, there are other well-marked and typical symptoms in that disease which must be due to a different cause. The frequency of pellagra without dermatitis in American experience makes it probable, seeing that a maize diet certainly plays less part in causing the disease in the United States than in Italy, that zeochin must be the chief factor of the skin trouble. But the dermatitis (which, moreover, may be aggravated, if not directly excited, by an excess of common salt and of acids in the diet) cannot be regarded as pathognomonic of pellagra. The most characteristic symptoms are the nervous disorders, which are obviously due to changes in the central nervous system. It must be admitted that we cannot as yet indicate any factor which has a peculiar selective influence such as is certainly exercised in pellagra upon the spinal cord and the great nerve trunks. Here, then, is an additional point that requires elucidation.

Perhaps the work of Urbeanu will prove of enormous importance in this connexion. My own innumerable observations of sick persons during the last twelve years have convinced me that a lack of bases in the diet impairs the

efficiency of the nervous system, the disorder being especially manifested in the form of neurasthenia and of migraine. These observations are in conformity with those of Hirschstein, who claimed moreover that in a particular case of migraine he obtained chemical proof that a deficiency of organically combined sulphur was a contributory cause. This lack of organically combined sulphur is likewise characteristic of the pellagrogenic diet, and it is certainly remarkable that proteins rich in cystin should be found especially valuable as ingredients of the remedial diet.

Perhaps a lack of bases in general, and a deficiency of calcium and potassium in particular, in conjunction with an excess of acids and a lack of organically combined sulphur, might in course of time induce the nerve degenerations characteristic of pellagra, especially if the before-mentioned faults in the diet were supplemented by the inadequacy of the protein it contained, by deficiency in respect of A, B, and D, and may be at times also by deficiency in respect of C.

CHAPTER TEN

CONCLUSION

As we have seen in the foregoing chapters, the data of the modern doctrine of nutrition are still dispersed in thousands of brief essays and reports. The mere collection of the writings most essential to the understanding of the subject is a formidable task. A further difficulty in securing a grasp of the material arises because in many cases an important fact never finds direct expression. Sometimes, being taken by the specialist as a matter of course, it is ignored and has to be read between the lines. Other facts, again, like that of the importance of an excess of bases in the diet, have escaped the notice even of the experts, and have to be discovered by a comparison of the details recorded in numerous investigations. We have no right, therefore, to reproach laymen (and as far as this subject is concerned, medical practitioners and the students of the chemistry of nutrients must be included among the laity) because their views concerning the modern theory of nutrition and the results of the experimental study of the physiology of nutrition are so confused and obscure —if, indeed, they have any opinions at all upon these topics.

But even the expert finds it extremely difficult to take a survey of the whole field, and the difficulty is especially conspicuous in connexion with the planning and carrying out of experiments. Thanks to the persistent endeavours of the American school, even here there has been a certain clarification during the last year, so that we may look forward to a greater uniformity in future results. Systematised methods have been formulated for the study of the various complettins, and have shown themselves to be of practical use; but their

application demands critical faculty, judgment, a knowledge of the literature, and wide practical experience.

1. Difficulties attendant on modern Experiments concerning Nutrition.

What applies to the more refined methods of chemical investigation, applies also to the experimental study of nutrition. An investigator may have given the most detailed accounts of his procedures, and one who endeavours to follow in his footsteps may be most scrupulous in the attempt to observe these prescriptions, and still the result may be unsatisfactory. Success cannot be guaranteed until methodological details have become automatic from long practice. Even the most proficient analyst will not have satisfactory results on the first occasion that he attempts to apply a complicated method. He has to make a number of trial experiments simply to secure familiarity with the technique.

In biochemical experiments upon nutrition the difficulties are, however, enormously greater than in ordinary chemical investigations, where the substance under examination is securely confined within the walls of a glass vessel. The material studied in the physiology of nutrition is the living organism with its infinitely manifold individual variations, which may be decisively modified by quite inconspicuous circumstances.

I have repeatedly insisted that in such studies an experiment lasting several months may still be too short to give trustworthy results, and that the whole lifetime of the animal under examination may not suffice. In such cases our only resource is to continue the experiment for several generations. If after five or six generations the development of the animals is still perfectly normal, we may then assume that the conditions of our trial experiments are in sufficiently close conformity with the conditions under which the animals in question live in a state of nature. Not until then can we safely proceed to ascertain the effect of withdrawing one of the constituents of the diet or of increasing the quantity of another.

But we must be extremely critical in our interpretation of the experiments when this stage has been reached. We are

not dealing with chemical constants, but with living beings; and although to our eyes they may seem as much alike as two prints from the same negative, they are really characterised by marked individual variations. If the number of the animals subjected to experiment be small, there is always a risk that the whole research may be invalidated by these chance variations. Not until the number of the experimental animals is considerable, can the experimenter be certain of avoiding such errors.

In this book there has been frequent occasion to mention the accidents that can interfere with experimental results. Let me remind the reader of the experiment on vitamin in which the animals ate their own faeces. This was an obviously unnatural practice which could not fail to be injurious to animals living under the free conditions of the struggle for existence, but in the actual circumstances of the experiment it saved their lives. Similar individual peculiarities are to be found in the greater or less faculty for procreation or conception, in the number of the young in a litter, and so on. The experimenter must be thoroughly familiar with all such possibilities if he is to avoid the most grotesque errors. In this connexion I must refer once more to the masterly experiments made by Robertson and Ray,[483, 487] which may serve as models for other experimenters. They paid the utmost attention to the conditions under which their mice were living. They provided admirably designed cages and food containers, avoiding the common errors of construction. Finally, they paid due attention to psychical influences, thinking out methods for the quick weighing of numerous animals together, and for the necessary handling of individual mice with the avoidance of anything that might induce shock. In their records they give a precise and detailed account of the development, the growth, the sexual life—in a word, the whole life-history—of the experimental animals.

But even attention to these details does not suffice, for each laboratory has its own specific peculiarities, and moreover there can be no doubt that the personality of the laboratory attendant who looks after the animals is a matter of considerable moment to their welfare. Although, therefore, it may be easy enough to instal in another laboratory the

apparatus designed by Robertson and Ray for investigations on mice, it will still be necessary, in these new surroundings, to study the undisturbed life-history of a great number of animals before proceeding to the actual experiment. The possibility of local variations must always be taken into account.

2. The Complettin Content of Foodstuffs.

Anyone making experiments as to the effect of complettins, must, of course, know where they are present, and approximately how much of them the various nutrients contain. But this question does not concern the laboratory experimentalist alone; it is perhaps even more important to anyone who has to prescribe diets for others. I am, in fact, besieged with queries on this subject, not only by doctors, but also by housewives and by the heads of institutions. I can hardly emphasise the importance of the matter better than by quoting a passage from Sherman and Smith's latest work.[1554] I should mention that until recently Sherman was one of the most zealous advocates of the protein-calorie doctrine!

"If we compare the human organism to an internal combustion engine (the traditional simile of the steam engine is inapt), the organic nutrients constitute the fuel, the protein and part of the inorganic nutrients form the materials out of which the engine is made, the rest of the inorganic nutrients represent the lubricating oil, and the complettins play the part of the spark. . . . All these substances are essential to the working of the machine. . . . In accordance with the law of the minimum, any one of them can function as the determining factor of the whole process. . . . In scientific experiments we may devote special attention to the supply of protein or to the provision of a sufficiency of calories. On the other hand, when we are practically planning a diet or considering the nutritive requirements of a family, we shall do better to make it our first aim to ensure the supply of a sufficiency of those nutrients which are known to us to be preeminent as conveyors of the necessary inorganic salts and the complettins. Not until then need we concern ourselves with the possibility that it may be necessary to supplement the diet in respect of protein or of energy by a further supply

of some suitable nutrient. Consequently, the person responsible for the diet must, above all, see to it that there shall be a sufficiency of milk, vegetables, and fruit, thereafter, cereals meat, fats, and sweetstuffs may be added according to the taste, the financial resources, and the digestive powers of the individual, and according to his needs in respect of energy. . . . Here is a good empirical rule in reckoning dietetical requirements. Spend at least as much upon vegetables and fruit, and at least as much upon milk, as you spend upon meat, fish, cereals, and sweetstuffs!" [Retranslated from the German.]

In preparing the following table I have made use of all the data known to me in the literature of the subject. The employment of the very latest results of research has led to considerable differences between my table and similar ones that have previously been published, but I think that my own is the most trustworthy issued to date. I describe the content of a complettin as "enough" when the quantity suffices, not merely to cure, but also to prevent a deficiency disease. When the content is so considerable that even very small quantities of the particular nutrient are effective, this content is described as "much." Amounts that are considerable, though not adequate, are denoted by the term "little." Insignificant amounts are described as "trace." A zero is used to indicate that no complettin can be detected. A query denotes that definite information is lacking (p. 328).

3. Nutrition in Complettin Experiments.

Numerous standard diets have been tabulated for use in the study of the various complettins. Seeing that again and again new dietetic factors requiring special attention have come to light, all the older prescriptions can unhesitatingly be discarded as obsolete. To-day, for researches concerning *the biological value of the different proteins*, the recommendations of B. Sure [1263, 1264] are those most worthy of consideration. For rats, he used an experimental diet consisting of dextrinised maize starch, Osborne's latest mixture of salts, clarified butter fat, and as conveyer of the water-soluble complettins an alcoholic extract of defatted wheat germs, while macerated agar was added as roughage. By present lights, a few improve-

FLESH-MEAT, FISH, EGGS.

	Vitamins	D	A	B	C
Muscular Tissue (fresh meat)	little	?	little	little	little
Tinned Meat	trace	trace	trace	trace	trace
Meat, frozen (not long in store)	little	little	little	little	little ?
Meat, frozen (long in store)	trace	?	trace	trace	trace
Meat, salt (not long in store)	little	?	little	little	little
Meat, salt (long in store)	a trace	?	trace	trace	trace
Brain	enough	?	little	enough	little ?
Heart	little	?	much	little	little ?
Kidney	enough	?	enough	enough	little ?
Liver	enough	?	much	enough	little ?
Spleen	little	?	little	little	o ?
Meat Extract	trace	?	trace	little	trace
Fish, lean	little	?	trace	little	o ?
Fish, fat	little	?	little	little	little ?
Fish, roe	enough	?	little	enough ?	little ?
Eggs (fowl's)	little	?	enough	little	trace ?
Egg (white of)	trace	?	trace	trace	trace
Egg (yolk of)	little	?	much	enough	trace ?

PULSES.

Beans, haricot (freshly dried)	much	much	little	enough	trace ?
Beans, haricot (old)	trace	?	trace ?	trace	trace ?
Beans, haricot (germinated)	trace	?	trace ?	trace	enough
French beans (fresh)	enough	enough	enough	enough	enough
Beans, soy	much	much	trace ?	much ?	trace
Beans, katjang-idjo	much	much	?	enough ?	?
Peas (ripe)	enough	enough	enough	enough	little ?
Peas (young green)	enough	enough	enough	enough	enough
Peas (germinated)	?	?	?	much ?	enough

CEREALS, SEEDS, FLOURS, BREAD.

Rye (whole grain)	enough	enough	little	enough	little ?
Rye (fine flour)	trace	?	trace	trace	trace
Rye (bread, wholemeal)	little	?	little	little	?
Wheat (whole grain)	enough	enough	little	enough	trace
Wheat (endosperm)	trace	?	trace	trace	trace
Wheat (germ)	much	much	little	much	trace
Wheat (bran)	much	much	little	enough	trace
Wheat (wholemeal)	enough	enough	trace	enough	trace
Wheat (bread, white, with water)	little	little	?	little	trace
Wheat (bread, white, with milk)	little	little	little	little	?
Wheat (bread, wholemeal, with water)	enough	enough	little	little	?

CEREALS, SEEDS, FLOURS, BREAD—*continued.*

	Vitamins	D	A	B	C
Wheat (bread, whole-meal, with milk) ..	enough	enough	enough	enough ?	?
Barley (whole grain) ..	enough	enough	little	enough	trace
Barley (groats) ..	enough	?	little	little	trace
Oats (rolled)	enough	?	little	little	trace
Malt (green)	enough ?	enough ?	little	enough ?	enough
Millet	enough	?	little	enough ?	o ?
Rice (unpolished) ..	much	enough	little	enough	trace
Rice (polished) ..	trace	?	trace	trace	trace
Maize (yellow, whole grain)	enough	?	little	enough	trace
Maize (white, whole grain)	enough	?	trace	enough ?	trace
Maize (fine flour, maizena)	trace	?	trace	trace	trace
Cotton seeds	enough	enough	little	enough	enough
Cotton seeds (fine meal)	enough	?	trace	trace	trace
Linseed	?	?	little	?	?
Hemp seeds	?	?	little	?	?
NUTS.					
Earth-nuts	enough	enough	little	enough	?
Hazel nuts	enough	enough	trace ?	enough	trace ?
Hickory nuts ..	enough	enough	trace ?	enough	?
Chestnuts (Spanish) ..	little	?	trace ?	enough	?
Cocoanut	enough	enough	little	enough	?
Cocoanut (cake) ..	much	much	trace	much	?
Almonds (sweet) ..	little	?	little	little	trace ?
Para nuts	enough	enough	trace	enough	trace ?
Pine kernels	little	?	little	little	?
Walnuts	enough	enough	trace ?	little	?
FRUITS.					
Apples	little	?	little	little	little
Oranges	enough	enough	little	much	much
Oranges (juice) ..	enough	enough	trace	enough	much
Bananas	enough	enough	little	enough	much
Pears	little	?	trace ?	little	trace ?
Cocum	?	?	?	?	little
Grape-fruit	enough	enough	?	enough	enough
Raspberries	?	?	?	?	much
Limes	little	?	trace ?	enough	little
Mangoes	?	?	?	?	little
Mulberries	?	?	?	?	little
Mulberries (dwarf) ..	?	?	?	?	much
Plums	little	?	?	little	?
Tomatoes	much	much	much	much	much
Tomatoes (boiled) ..	much	much	much	much	much
Grapes	enough	enough	?	enough	enough
Grape juice	little	?	little ?	little	enough
Lemons (ripe) ..	enough	enough	little	enough	much
Lemons (green) ..	much	much	much	much	much

FRUITS—*continued.*

	Vitamins	D	A	B	C
Lemons (juice of commerce)	?	?	?	?	enough
Tamarinds (dried) ..	?	?	?	?	little
ROOTS AND TUBERS.					
Sweet potatoes ..	little	little	enough	little	trace
Potatoes (raw) ..	enough	enough	little	enough	much
Potatoes (boiled for one hour)	enough	enough	little	enough	enough
Potatoes (dried) ..	enough	enough	little	enough ?	little
Carrots (raw) ..	enough	enough	enough	enough	enough
Carrots (boiled) ..	little	little	enough	little	little
Carrots (juice) ..	much	much	enough	much	much
Parsnips	enough	enough	little	enough	?
Radishes	little	?	trace ?	little	trace ?
Beetroots	little	?	?	little	?
Turnips	enough	enough	little	enough	much
Kohlrabi	enough	enough	enough	enough	much
Mangel-wurzels ..	enough	enough	enough	enough	enough
Swedes	enough	enough	trace ?	enough	much
GREEN VEGETABLES, LEAVES, ETC.					
Artichokes	little	?	enough	little	?
Lucerne	much	much	much	much	much
Green leaves	much	much	much	enough	enough
Cauliflower	enough	enough	little	enough	little
Dasheen	little	?	trace	little	little
Egg-plant	enough	enough	?	enough	trace
Grass	enough	enough	much	much	enough
Green cabbage ..	enough	enough	much	much	much
Cucumber	little	?	?	little	much
Hay	enough	?	enough	enough	trace
Clover (fresh)	much	much	much	much	much
Lettuce	enough	enough	enough	enough	much
Cresses	?	?	?	?	little
Timothy grass ..	enough	enough	much	much	enough
Dandelion leaves ..	enough	enough	much	enough	enough
Rhubarb (stalk) ..	?	?	?	?	little
Pickled cabbage (Sauerkraut)	?	?	?	?	?
Celery	?	?	?	little	?
Spinach (raw) ..	much	much	much	much	much
Spinach (boiled) ..	enough	enough	much	enough	enough
Spinach (dried) ..	enough	enough	much	enough	trace
Pumpkin (squash) ..	?	?	enough	?	?
White cabbage (raw) .	much	much	enough	much	much
White cabbage (boiled)	enough	enough	enough	enough	enough
White cabbage (dried)	enough	enough	little	enough	little
Onions	enough	enough	trace	enough	enough
MILK AND MILK PRODUCTS					
Human milk	enough	enough	much	enough	enough
Cow's milk	enough	enough	much	enough	variable

MILK AND MILK PRODUCTS—*continued.*

	Vitamins	D	A	B	C
Cow's milk (scalded only)	enough	enough	much	enough	variable
Cow's milk (pasteurised)	little	little	much	little	trace
Cow's milk (condensed)	enough ?	enough ?	much	enough ?	trace
Cow's milk (dried slowly)	trace	?	much	trace	trace
Cow's milk (dried instantaneously)	enough	enough	much	enough	variable
Cow's milk (skim-)	enough	enough	little	enough	variable
Cow's milk (butter-)	enough	enough	little	enough	variable
Butter	trace	?	much	trace	trace ?
Cream	enough	enough	much	enough	variable
Cheese (skim-milk)	trace	?	little	?	?
Cheese (full-milk)	trace	?	enough	?	?
FATS AND OILS.					
Cottonseed oil	?	?	little	?	?
Egg fat	o	o	much	o	o
Earth-nut oil	o	o	trace	o	o
Fish oil	o	o	much	o	o
Cocoanut oil	o	o	trace	o	o
Codliver oil	o ?	o ?	much	o ?	o
Linseed oil	o	o	trace	o	o
Maize oil	o	o	little	o	o
Almond oil	o	o	trace	o	o
Margarine (vegetable)	o	o	trace	o	o
Margarine (animal)	o	o	little	o	o
Nut oil	o	o	trace	o	o
Oleomargarine (olein)	o	o	little	o	o
Olive oil	o	o	trace	o	o
Orange-peel oil	trace ?	trace ?	enough	trace ?	trace ?
Palm oil	o	o	little	o	o
Horse fat	o	o	little	o	o
Beef fat	o	o	little	o	o
Mutton fat	o	o	little	o	o
Pig fat (kidney fat)	o	o	enough	o	o
Pig fat (lard)	o	o	trace	o	o
Suet	o	o	little	o	o
Stearin	o	o	trace	o	o
Whale oil	trace ?	?	enough	trace ?	o
YEAST PRODUCTS.					
Yeast	much	much	much	trace	trace
Yeast (dried)	enough	enough	trace	enough	trace
Yeast (extract)	much	much	trace	much	trace
SUGARS AND STARCHES.					
Sugar (refined)	o	o	o	o	o
Honey	little	o ?	o	o	o
Honey (artificial)	o	o	o	o	o
Starch	trace	o ?	o	o ?	o

ments might be suggested. Potato starch would be preferable to maize starch, for the latter contains traces of colouring matter which might prove injurious (especially to white mice and white rats). The salt mixture could be bettered by increasing the dose of calcium carbonate to about 170 grammes; the small quantity of manganese sulphate should be replaced by 10 grammes of manganese citrate; the magnesia should be increased to 20 grammes; the phosphoric acid should be reduced to 60 grammes; and, finally, 5 grammes of crystalline sodium silicate should be added to the mixture. It still remains to be decided whether this mixture will prove adequate for several successive generations of the experimental animals. (See next paragraph.) The use of wheat germs instead of the yeast extract that has hitherto been customary is not a desirable change, for we have seen that wheat germs are comparatively poor in complettins. Better than either would be an extract of young clover not yet flowering or of young spinach, precipitated with alcohol to get rid of the proteins and then heated for a short time to 60° C. Of course all these extracts contain amino-acids, which must on no account be left out of the reckoning.

In experiments on the *inorganic nutrients*, the protein of the diet should be supplied in the form of carefully purified casein and lactalbumin; the other constituents of the food should be pure potato starch, macerated agar, clarified melted butter fat, and the improved salt mixture just described. Special series of experiments should immediately be undertaken to ascertain whether the experimental animals can really thrive for a number of generations without a trifling addition of copper and zinc to the diet. In experiments upon the various forms of combination of phosphoric acid and of sulphur, it must not be forgotten that the proteins and the butter contain these substances, and that the amount of them in the macerated agar is by no means negligible. The experimenter must also bear in mind that the most sedulously purified nutrients always contain quantities of ash which may in certain circumstances be of decisive importance. Let me remind the reader of what was said in the third chapter anent the phosphorus content of edestin, and also of my own experience that purified fats invariably contain organically

combined sulphur. Hence it is perhaps better to use a chemically pure filter paper as roughage.

In experiments upon the action of the *real vitamins* (Funk's), difficulties arise which have been especially stressed by Simonnet.[1301] Hitherto these experiments have usually been made with nutrients which in other respects were extremely inadequate, and it is doubtless for this reason that the morbid anatomy of beriberi and experimental polyneuritis is so diversified. Simonnet recommends the following experimental diet: meat, thoroughly boiled and pressed, then extracted twice with boiling alcohol and once with ether, 11 grammes; Osborne's salt mixture, 4 grammes; agar powder, 5 grammes; earth-nut oil, 5 grammes; butter fat, 10 grammes; quantitative filter paper, 5 grammes; potato starch, 60 grammes. After mixing with 80 % of distilled water, the mixture is given to pigeons by cramming, the daily allowance amounting to half the weight of the birds. Both B and C are lacking in this mixture as well as vitamin; but the lack of B and C is of comparatively little importance, for it has not time to make itself felt owing to the rapid development of the consequences of vitamin deficiency. There is, however, one grave defect in Simonnet's recommendations; they take no account of the difference in the respective effects of vitamins and the water-soluble antineuritic D. The problem of the origin of the various forms of polyneuritis cannot be solved without the recognition of this difference. We have learned that the two classes of substances unquestionably make their lack felt in different parts of the organism. As yet we have no trustworthy method by which Funk's vitamin and water-soluble D can be wholly separated each from the other, and in this department of the research the discovery of such a method must be our immediate task. Next comes an additional point to be considered. It has hitherto been assumed that the lack of B in these experiments is of no moment, for the incubation period of polyneuritis is so short that B deficiency cannot make itself felt. It is nevertheless possible that even in so brief a period the lack of B may take effect, especially upon the glands. Moreover, we have already noted that C deficiency is probably the cause of the trifling haemorrhages sometimes met with in cases of

polyneuritis. We must, therefore, endeavour to discover ways and means of freeing B and C from vitamins and the water-soluble antineuritic D, so that a sufficiency of B and C may be added to the experimental diet.

When studying the *conditions of growth*, the experimenter will naturally regulate the experimental diet with an eye to the special problem under examination, but he must take the utmost care that in other respects the diet shall be adequate. A study of the fat-soluble complettin is a fairly easy matter, for this complettin is readily destroyed by oxidising agents. But it must not be forgotten that the complettin C, whose presence in the diet is absolutely indispensable in these cases, is likewise sensitive to oxidising agents, and may therefore be destroyed by the methods used for the removal of A. Similar and more formidable difficulties arise in the study of the effects of B, for the means employed to free the diet from B are apt to destroy D and C as well. There is still a good deal to be cleared up in connexion with such matters, and much further work will be requisite before it will be possible to provide a throughly satisfactory experimental diet suitable for each particular type of investigation. As an example of the technique of these investigations, I may refer to Osborne and Mendel's latest publication,[1331] with the remark, however, that the diet there mentioned is designed solely with regard to the fat requirements of the experimental animals, and contains a source of fallacy even there. Dried, pulverised meat cannot be completely defatted by extraction with alcohol and ether, and in the prescribed diet the meat powder of the daily ration will still contain about 0·4 grammes of fat.

Byfield, Daniels, and Loughlin [1153] tabulate an excellent fundamental diet which they suppose to be satisfactory even in respect of the absence of the water-soluble complettins. But they were investigating the problem as to whether vitamin and B are identical, and obviously the diet they recommend is quite unsuitable for the purposes of this investigation, seeing that the deficiencies of vitamin, B, C, and D reinforce one another. Moreover, in experiments on growth-factors, casein should not be the only source of protein, seeing that this protein is not wholly adequate for the growing organism.

We must either give an approximately equal quantity of lactalbumin in addition, or else, following Osborne and Mendel's example, use meat protein purified as thoroughly as possible.

An experimental diet for the study of the effects of *B-containing extracts* is not difficult to arrange. It should consist of meat that has been pressed and thoroughly boiled and subsequently extracted with alcohol and ether, starch similarly extracted, salt mixture, and filter paper. The allowance of fat must be kept for several hours at a temperature ranging from 120° to 130° C. with air passing through it all the time, to free it from A. As conveyer of the water-soluble complettins, a vegetable extract will be used, freed from A by extraction with alcohol and ether. The small quantities of vitamin or of water-soluble complettins which may pass off in solution when the inspissated extract is being extracted in vacuo are negligible provided a sufficient amount of the extract be added to the diet.

For the study of the effect of the *antiscorbutic complettin C*, it is likewise comparatively easy to arrange a diet that shall be adequate in other respects. This diet will consist of pure proteins, dextrinised starch, a fat (preferably butter fat as conveyor of A), filter paper, and salts. As conveyers of the other water-soluble complettins, we shall use an expressed vegetable juice, spinach juice for instance, in which the C has been destroyed by evaporation to dryness in vacuo at a temperature ranging from 60° to 70° C.

The foregoing indications as to experimental diets have no claim to completeness. They are merely intended to show that, despite the elaborately developed technique, the difficulties to be reckoned with in these experiments are still extensive; and to show, further, that all the problems are still in a state of flux. A great deal more work will have to be done before we shall possess an unexceptionable technique even for one branch of these investigations. It is, therefore, rather remarkable that Aron and Gralka [1386] should declare it to be the duty of investigators henceforward, not only to determine (as heretofore) the amount of protein, fat, carbohydrates, and inorganic salts the nutrients contain, but to ascertain also by experiments on animals the biological value

of these nutrients as regards protein, fat, and complettins. Aron seems to have no idea of the amount of work that is already imposed upon those who are studying the biochemistry of nutrition, and he fails to realise the scantiness of their resources. For such investigations as he recommends it would be necessary to have a regular zoological garden with a highly trained staff. No private investigators have anything of this sort at their disposal, nor as yet can official research laboratories command anything like it. One who reads Aron and Gralka's paper cannot but feel ironical when he notes that even so distinguished an investigator as Aron himself is obviously unacquainted with the most important researches of the last two years. In especial it must be mentioned that the salt mixture recommended by Aron is quite inadequate. Furthermore, he suggests plasmon as a source of protein, but in long-continued experiments this protein proves inadequate.

4. The immediate Problems of Complettin Research.

What are the immediate tasks of complettin research? They are as follows: further study of the biological value of the various proteins used as nutrients; an examination as to how far there is a vital need for certain inorganic substances universally present in natural food, but present only in very small quantities; the differentiation of Funk's vitamins from the antineuritic complettin D, and from the growth-factor B; a study of the function of the fat-soluble complettin A in the organism of growing animals and adults respectively; finally, the isolation of the complettins in a pure state. Further, it will be eminently desirable, in all these researches, to seek the aid of experts in pathological anatomy, so that we may ascertain the precise effect upon the organs and tissues resulting from a lack of the various complettins. This knowledge would be of the greatest value to therapeutics. Finally, I must insist once more that the methods hitherto employed for the analytical determination of the inorganic constituents of the diet, whether employed by biologists, medical practitioners, or biochemists, have been inadequate and misleading. The Experimental Stations Office in Washington, U.S.A., has recently endorsed this criticism. The utmost accuracy is essential in such investigations.

5. The Need for State Aid in Experiments on Nutrition.

It is obvious that these problems can only be studied with success in great institutes, with the aid of large laboratories and extensive zoological gardens, with that of a staff of analytical, biological, and anatomical experts, and a number of well-trained subordinate assistants. These requisites are not fulfilled at the extant institutes attached to the universities, for there the personnel of the staff changes so rapidly that the trustworthiness of the results is endangered. What we need is the foundation of large institutes with permanent staffs whose members have an assured position. In the United States such places may be provided by the munificence of millionaires; but in impoverished Europe, and especially in Germany, we must look to the State for aid. In such matters, thrift is out of place. Every day demands its sacrifice of the public health through errors of diet, and thereby the whole body politic is enfeebled.

But it will not suffice that steps should at length be taken to throw light upon the biological processes of nutrition. Of what avail would it be that scientific experts are fully informed concerning these matters, so long as the great mass of the population is being ruined in health by irrational feeding? *In addition to institutes for the biochemical study of nutrition, there must be institutes of nutritive hygiene whose task it will be to ensure the practical application of the theoretical acquisitions of biochemistry, to ensure that the data of the new science of nutrition shall be realised in daily life. The consciousness of the masses must be permeated with a practical knowledge of the new science of dietetics.*

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